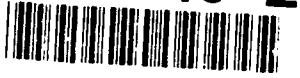

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POLYCHLORINATED BIPHENYLS (PCBs), POLYCHLORINATED DIBENZOFURANS (PCDFs), AND POLYCHLORINATED DIOXINS (PCDDs)

NAVY ENVIRONMENTAL HEALTH CENTER

BUREAU OF MEDICINE AND SURGERY

Reviewed and approved in accordance
with SECNAVINST 5600.16A

CAPTAIN J.J. EDWARDS, MC, USN
Commanding Officer

POLYCHLORINATED BIPHENYLS (PCBs), POLYCHLORINATED DIBENZOFURANS (PCDFs), AND POLYCHLORINATED DIOXINS (PCDDs)

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This manual is intended to familiarize the industrial hygienist with the information that is most salient to understanding the health hazards related to occupational exposure to PCBs and their structural analogs, the furans and dioxins. A short summary of the regulations and standards which have been issued to date by the EPA, OSHA, NIOSH, and the ACGIH is included, as is a cursory review of the literature related to toxicological effects in animals and humans. General descriptions of sampling methodologies, a review of control practices, including required personal protective equipment, and NAVOSH requirements for medical surveillance are included to provide guidance to Navy health and medical personnel.

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INTRODUCTION

The family of compounds collectively called polychlorinated biphenyls (PCBs) have been considered, since the 1970's, to be hazardous chemicals, posing potential hazard both to the environment and to human health. The chemical nature of PCBs so closely resembles one of the most persistent and infamous environmental pollutants, dichlorodiphenyltrichloroethane (DDT), that scientists and government regulators alike viewed with alarm the high rate of usage and widespread dispersal of the chemicals throughout developed countries up to that time. When data showing that PCBs exhibited DDT-like persistence in the environment first surfaced (Jensen, 1966), federal agencies and other authorities tasked with environmental protection initiated measures to regulate the compounds.

In 1968 an industrial accident in western Japan irrevocably altered the scientific community's perception of PCBs; in that incident, over a thousand civilians were poisoned by using cooking oil which had been contaminated with PCBs during a heat-purification process. Prior to the "Yusho" (meaning "cooking oil") incident, the only human health hazard associated with PCBs was a type of occupational skin rash known as chloracne; the symptoms associated with the Yusho incident were much more serious, and included hepatological and possible teratogenic effects. The "Yusho" incident forced the recognition that PCBs could, under some circumstances, pose serious hazard to human health. The regulation of the compounds was extended to the realm of industrial hygiene.

In the years between 1970 and the present, a considerable amount of research has been focused on elucidating the true hazard presented by PCBs. It has proved to be no trivial task. As this bulletin will describe, the analytical methods employed for PCB determinations are by no means straightforward "cookbook" operations: basic assumptions must still be incorporated into the protocols, and the resultant values are highly dependent on the choice of assumptions. Moreover, the lack of an absolute standard still plagues researchers and renders two decades of data ambiguous. Compounding these difficulties is a basic complication common to many toxic compounds - human studies cannot be performed; inferences from animal studies must be used to assess human hazards, and species-specific differences in sensitivity lends further ambiguity. Epidemiological studies, conducted primarily after major incidents, are open to criticism due to the absence of quantitation of initial levels of contamination. Due to all of these complexities, global conclusions by reviewers have differed markedly, and federal regulations currently reflect the lack of definition.

This manual is intended to familiarize the industrial hygienist with the information that is most salient to understanding the health hazards related to occupational exposure to PCBs and their structural analogs, the furans and dioxins. A short summary of the regulations and standards which have been issued to date by the EPA, OSHA, NIOSH, and the ACGIH is included, as is a cursory review of the literature related to toxicological effects in animals and humans. General descriptions of sampling methodologies, a review of control practices, including required personal protective equipment, and NAVOSH requirements for medical surveillance are included to provide guidance to Navy health and medical personnel.

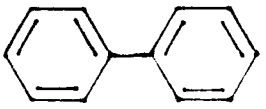
CHEMICAL AND PHYSICAL PROPERTIES OF PCBs AND RELATED FURANS AND DIOXINS

CHEMICAL AND PHYSICAL PROPERTIES

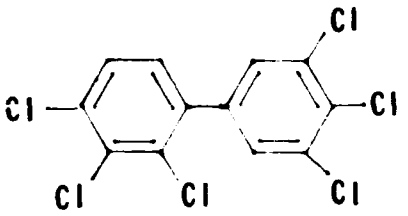
Two significant features of PCBs that the industrial hygienist should be acquainted with are: (1) PCBs are very stable compounds (their lack of reactivity is a highly desirable feature for industrial applications); (2) PCB solutions are not composed of a single chemical compound, but are a heterogeneous mixture of a number of compounds all belonging to the same family.

The low reactivity of PCBs is related to the chemical structure of the unsubstituted base molecule, bi-phenyl (shown below). The two planar benzene rings are themselves quite unreactive; when from one, to a possible ten, of the hydrogens on the two phenyl rings are substituted with chlorine, the reactivity is proportionally lowered.

BIPHENYL



POLYCHLORINATED BIPHENYL
(Hexachlorobiphenyl)



Commercial PCB solutions are not single-component products containing one chemical; rather, they are a blended product, containing 50-80 percent "pure" PCB solution, and 50-20 percent diluent; the diluent is commonly an organic solvent such as mineral oil or chlorobenzene. Nor is that portion of the mixture which is considered "pure" PCB solution the liquid phase of a single chemical species, such as, for example, pentachlorobiphenyl. Rather it is a mixture of many chlorinated biphenyl species, with varying proportions of the mono-, di-, tri-, and so forth- chlorinated molecules. This occurs because the synthesis reactions that produce PCBs produce a range of chlorinated products; reaction conditions can be altered to produce a predominance of one species, but not a single species. Since mixtures of PCB isomers have no negative effect on industrial applications, exhaustive separation procedures are not required. (The primary disadvantage of isomer mixtures is related to assaying for the product).

Since from one to ten positions of the two biphenyl rings can be chlorinated, many PCB products are possible. The chemical names, formulas, and molecular weights of some common polychlorinated biphenyls are given below. Note that molecules with from one to nine positions chlorinated will have several possible

isomers, because of the number of geometric locations possible for the chlorines; thus there are 209 possible PCB isomers.

POLYCHLORINATED BIPHENYLS

Name	Formula	Mol. wt.	# Isomers
Chlorobiphenyl	$C_{12}H_9Cl$	188.7	3
Dichlorobiphenyl	$C_{12}H_8Cl_2$	223.1	12
Trichlorobiphenyl	$C_{12}H_7Cl_3$	257.6	24
Tetrachlorobiphenyl	$C_{12}H_6Cl_4$	292.0	42
Pentachlorobiphenyl	$C_{12}H_5Cl_5$	326.4	46
Hexachlorobiphenyl	$C_{12}H_4Cl_6$	360.9	42
Heptachlorobiphenyl	$C_{12}H_3Cl_7$	395.3	24
Octachlorobiphenyl	$C_{12}H_2Cl_8$	428.7	12
Nonachlorobiphenyl	$C_{12}HCl_9$	464.1	3
Decachlorobiphenyl	$C_{12}Cl_{10}$	498.5	1

Commercially available PCB mixtures are specified according to the overall percentage (by weight) of chlorine present. Approximate percentages of chlorination in some commercial PCB mixtures (in this case Arochlors, produced by Monsanto) are as follows:

Number of Chlorines	AROCHLOR 1221	1231	1016	1242	1248	1254	1260
0	9	6	Tr	Tr	--	--	--
1	51	26	1	1	Tr	Tr	--
2	35	29	20	12	1	Tr	--
3	4	24	57	43	23	1	--
4	1	15	21	33	50	24	--
5	Tr	Tr	1	11	20	51	12
6	--	--	--	Tr	1	21	46
7	--	--	--	Tr	--	3	35
8	--	--	--	--	--	--	6
9	--	--	--	--	--	--	--
10	--	--	--	--	--	--	--
Percentage of Chlorine (by weight)	21%	31%	42%	42%	48%	54%	60%

- Trace is abbreviated as "Tr".

- The information shown above was compiled from a number of different sources; individual Aroclor mixtures may vary.

PCB mixtures are generically referred to as "congeners" (meaning, "belonging to the same class of compound"), or as "Aroclors" (after a trade name). Common trade names of PCBs (and country of manufacture) include:

Aroclor	USA	Fenclor	Denmark
Aroclor B	USA	Hyvol	France
Asbestol	USA	Inerteen	USA
Askarel	USA	Kaneclor	Japan
Chlorextol	USA	No-Flamol	USA
Chlorinol	USA	Phenchlor	France
Clophen	FRG	Pyranol	USA
Diaclor	Japan	Saf-T-Kuhl	USA
Dykanol	USA	Sovol	USSR
Elemex	USA	Therminol	USA

- Phenchlor DP6 (made in France) and Clophen A60 (made in West Germany) are almost identical in composition to Aroclor 1260.

- Fenclor (made in Denmark) is 100% decachlorobiphenyl.

- Kanechlors (Japanese products) are similar, in degree of clorination, to American Aroclors; for example:

KC-300 is similar to Aroclor 1016
KC-400 is similar to Aroclor 1248
KC-500 is similar to Aroclor 1254

At room temperatures "pure" PCBs are highly viscous, and have about the consistency of gelatin. For industrial uses, it is generally desirable to reduce the viscosity; this is accomplished by dilution with organic solvents. The solvents used are typically mineral oil or mono-, tri-, and tetra-chlorinated benzenes. Selected properties of several chlorinated benzenes are listed below:

	CHLORINATED BENZENES		
Property	Mono-	Tri-	Tetra-
Molecular Weight	112.6	181.5	215.9
Boiling Point (°C)	132	209-221	243-254
Vapor Pressure (mm Hg)	8.8	1-10	<0.1
Flash Point (°C)	29	107-113	155

The notable physical and chemical characteristics of PCBs include thermal stability, resistance to oxidation, low reactivity with acids, bases, and other chemical agents, and excellent dielectric (insulating) properties. PCBs are highly soluble in oils and organic solvents. They are also soluble in water, which is a factor in their versatility. Water solubilities of PCBs range from 0.007 - 5.9 mg/liter (Hutzinger, 1974).

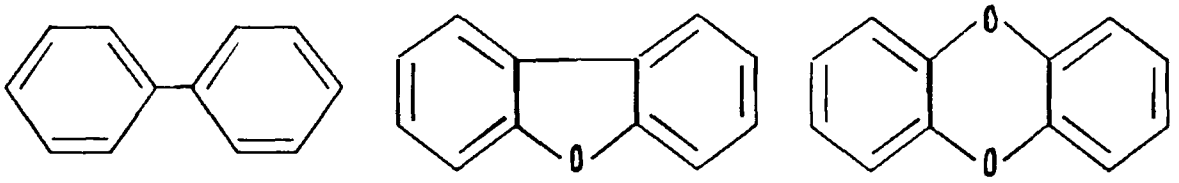
Other physical properties are provided below:

	AROCHLOR				
Property	1221	1242	1248	1254	1260
Distillation Range (°C)	275-320	325-366	325-366	365-390	385-420
Vapor Pressure (mm Hg)	---	0.001	0.00037	0.00006	---
Flash Point (°C)	141-150	176-180	193-196	None	None

FURANS AND DIOXINS

Dibenzo-furans and -dioxins are structurally similar to the biphenyls; having the same two phenyl rings, these molecules can be chlorinated to various degrees, just like the PCBs. The structural formulas of the unsubstituted dibenzo-furan and dibenzo-para-dioxin base compounds are given below:

(BIPHENYL) **FURAN** **DIOXIN**



Dibenzo-furans and -dioxins are found as trace contaminants in PCB products; they are derived as side products in the PCB manufacturing process. Studies have shown that the concentration of these contaminants can range from as low as 1 to as high as 500 ug/gm of PCB (Milby, 1985).

The chemical names, formulas, and molecular weights of some common poly-chlorinated dibenzo-furans (PCDFs) and poly-chlorinated dibenzo-dioxins (PCDDs) are given below; note the similarily between these compounds and the family of PCBs provided previously:

POLYCHLORINATED FURANS AND DIOXINS

Name	Formula	Mol. wt.	#Isomers
Chlorodibenzofuran	$C_{12}H_7ClO$	202.7	4
Dichlorodibenzofuran	$C_{12}H_6Cl_2O$	237.1	16
Trichlorodibenzofuran	$C_{12}H_7Cl_3O$	271.6	28
Tetrachlorodibenzofuran	$C_{12}H_6Cl_4O$	306.0	38
Pentachlorodibenzofuran	$C_{12}H_5Cl_5O$	340.4	28
Hexachlorodibenzofuran	$C_{12}H_4Cl_6O$	374.9	16
Heptachlorodibenzofuran	$C_{12}H_3Cl_7O$	409.3	4
Octachlorodibenzofuran	$C_{12}H_2Cl_8O$	442.7	1
Chlorodibenzo-p-dioxin	$C_{12}H_7ClO_2$	218.7	2
Dichlorodibenzo-p-dioxin	$C_{12}H_6Cl_2O_2$	253.1	10
Trichlorodibenzo-p-dioxin	$C_{12}H_7Cl_3O_2$	287.6	14
Tetrachlorodibenzo-p-dioxin	$C_{12}H_6Cl_4O_2$	322.0	22
Pentachlorodibenzo-p-dioxin	$C_{12}H_5Cl_5O_2$	356.4	14
Hexachlorodibenzo-p-dioxin	$C_{12}H_4Cl_6O_2$	390.9	10
Heptachlorodibenzo-p-dioxin	$C_{12}H_3Cl_7O_2$	425.3	2
Octachlorodibenzo-p-dioxin	$C_{12}H_2Cl_8O_2$	458.7	1

*There are 135 possible PCDF isomers, and 75 possible PCDD isomers.

Polychlorinated furans and dioxins are important to PCB chemistry and toxicity for several reasons. PCDFs and PCDDs are much more potent, toxicologically, than PCBs. Low levels of contamination with these products may thus significantly alter the physiological responses recorded in "PCB" studies. Also, under certain conditions such as industrial fires or explosions, furan and dioxin products can be generated from PCBs. As data on PCDF and PCDD generation and toxicity have been accumulated in the last two decades, it has become apparent that the degree of contamination with these products is a vital parameter in the overall hazard presented in "PCB" industrial accidents.

Since all PCB solutions contain some degree of furan and dioxin contamination, researchers need a method of recording such levels. Although there is still debate on the matter, dioxin and furan levels are generally discussed in terms of "dioxin equivalents." A "dioxin equivalent" is a summation of all the isomers of dioxins and furans found in a particular solution; it is a numerical value which includes a weighting factor to compare the potency of the isomer mixture with "pure" dioxin (i.e. with 2,3,7,8-tetrachlorinated dibenzo-p-dioxin).

Dioxins and furans can be generated when PCBs and chlorinated solvents undergo pyrolytic reactions (chemical reactions involving heat). The quantity and type of dioxin/furan generated is highly dependent on the temperature, type of Aroclor, and type of solvent being pyrolyzed. For example, if PCBs and chlorinated benzenes are heated to temperatures of 550 to 650 °C, in the presence of oxygen, the predominant by-products will be furans; dioxins will also be formed, but to a far lesser degree. If, on the other hand, the same reactants are heated to 700 °C, very little if any furan will be formed, as the pyrolsis reaction goes on to completion (Buser, 1979). Furans in low concentrations have been found in pressurized releases at temperatures as low as 300°C.

The production of PCDFs and PCDDs from PCB solutions under special circumstances is important to industrial hygiene considerations primarily because of the nature of certain industrial applications: PCBs are commonly used in capacitors and transformers in the utilities industry. In this role they are necessarily coupled with electrical sources, and thus are subject to conditions which are conducive, or at least vulnerable, to fires or explosions. When transformers containing PCBs explode, PCBs are released, and in addition, furans and dioxins are generated.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURE ISSUES

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURE ISSUES

Environmental Pollution

PCBs, dioxins and furans have become ubiquitous environmental pollutants, and can be found almost anywhere. A recent Canadian study found that PCBs, dioxins and furans were present in most domestic foods: the compounds were found in meats as well as in fruits and vegetables (Davies, 1988). The Environmental Protection Agency recently revealed that significant concentrations of dioxins are present in white paper products - apparently produced during the bleaching process (Keenan, 1989). Low levels of PCBs are found in ocean waters and even in Artic ice (National Academy of Sciences, 1979; Tanabe, 1983). An even more sobering fact is that PCBs have been found, in measureable concentrations, in both blood serum and breast milk samples collected from non-occupationally exposed persons residing in such diverse locations as Japan, South Carolina and Colorado (Savage, 1973).

Prior to 1970, PCBs were entirely unregulated in the United States and Europe; they were generally considered to be innocuous compounds, and their chemical and thermal stability made them ideal for industrial applications. It would be difficult to overstate the magnitude of PCB utilization by industry between 1930 and the mid-1970's. Literally thousands of tons of PCBs were utilized yearly in the United States alone. This was due to the fact that PCBs were extensively employed in the utilities and plastics industries. PCBs were used as plasticizers in the production of essential construction plastics such as vinyl chloride. PCB compounds were also used in the production of fire retardants, adhesives, waterproof wall coatings, surface treatments of textiles and surface coatings of wood, in caulking materials, paints, and printing inks, in hydraulic fluids and cutting oils, in microscope immersion oils and in carbonless copy paper. But by far, the greatest use of PCBs was in the utilities industry, where they were used as dielectric fluids in transformers and capacitors (IARC, 1978).

Today, PCBs cannot be manufactured or transported in the United States unless special exemptions have been obtained; products cannot contain PCBs unless they are entirely sealed units, and stringent environmental standards apply (40 CFR Part 761). To understand why the status of PCBs has been so drastically altered one must recognize the historical context in which they were first recognized as environmental pollutants and potentially hazardous to human health.

By the 1960's DDT had become possibly the most infamous pesticide in the world, and was recognized both as an environmental pollutant and a potent toxin that had wreaked havoc on many wildlife species due to biomagnification in the food chain. In

1966 a Swedish researcher was collecting data on DDT in coastal Norwegian waters. Using more sophisticated equipment than previous researchers, he found substances which were similar to DDT in all the ocean water samples and fish specimens that were assayed. Further identification proved that these substances were PCBs (Jensen, 1966). When these findings were published, the scientific community had good reason to be alarmed: PCBs had been used in larger quantities, and for a longer period of time that DDT. Like DDT, PCBs were stable compounds, and under normal conditions could be expected to remain undegraded and persist in the environment for years. If PCBs were not innocuous compounds, as was previously supposed, could they not present significant hazard to wildlife and/or human health?

Evidence that PCBs could be hazardous to human health was abruptly provided with the occurrence, in 1968, of the "Yusho" incident in Japan. Over a thousand Japanese civilians were poisoned when they ingested rice bran cooking oil that had inadvertently been contaminated with PCBs. The contamination had occurred during a heat purification process, during which the rice bran oil had been heated by means of heat-exchanger pipes. The heat transfer fluid in the pipes was PCB; the pipes were old, and had pinpoint holes which leaked PCBs into the rice bran oil. Ingestion of the cooking oil caused serious health effects in the subject population: symptoms included chloracne, discoloration of the gums and nailbeds, swelling of the joints, waxy secretions of the glands in the eyelids, lethargy and joint pain.

Human Health Hazard

When PCBs were identified as the causative agent of the "Yusho" epidemic, both environmentalists and health officials in the United States were convinced that regulatory intervention was warranted. In reaction to the Yusho incident, the U.S. Food and Drug Administration (FDA) initiated a national survey to determine the extent to which U.S. food sources had been contaminated with PCBs. The survey showed that less than 5% of the animal feed samples assayed contained any level of PCBs, however, because PCBs were found, in several isolated instances, in eggs, poultry, and milk, the FDA decided to limit the amount of PCBs which could enter the food chain. A "Notice of Proposed Rule Making" was published and subsequently temporary tolerances were established for fish and food products (Federal Register, 1972 and 1973).

Because the temporary tolerance levels were to be used "until such time as toxicological data suggested reconsideration", a great number of research efforts were undertaken in the next several years to assess the toxicity of PCBs; numerous animal toxicity studies were performed, as were epidemiological studies of populations working in or residing near PCB plants. In an effort to assimilate and review the data thus generated the EPA sponsored a "National Conference on PCBs" in 1975. Although most

of the epidemiological studies provided inconclusive results, animal toxicity studies, primarily structured to evaluate ingestion hazards, showed significant correlation between ingestion of PCBs and a variety of adverse effects, ranging from hepatotoxicity (enzyme induction and degenerative liver alterations) to possible teratogenicity (Higuchi, 1976; cited in Gaffey, 1984). Subsequent to the conference the FDA lowered the tolerance levels for food products, and the EPA issued rules governing the use of PCBs in specific industrial applications.

Under the Toxic Substances Control Act of 1976, the EPA proposed that plants manufacturing or processing food, drugs, or cosmetics discontinue use of PCBs in heat transfer applications. This Act marked the first instance in which PCB regulations were imposed on industrial processes. Over the next several years PCB regulations became progressively more restrictive, and were expanded in scope to include industries other than food processing or manufacturing. In response, many industries switched to substitute materials, or ceased production of PCB-containing products. However, the enormous utilities industry could not convert to substitute materials so easily - PCBs had been the specified fluid for millions of transformers and capacitors produced in the previous two decades. Occupational exposure to PCBs in capacitor manufacturing plants and in occupations requiring contact with transformers thus became an issue of concern to regulators. Many of the current PCB regulations are related to transformer fluids.

Occupational Exposure to PCBs from Transformer Fluids

The potential for exposure from PCBs in transformers was clearly exemplified in the 1980's, when several catastrophic transformer fires occurred in the U.S. - in Binghamton, NY (1981), San Francisco (1985), Tulsa (1985), and Sante Fe (1986). These incidents were large scale, produced significant PCB contamination, and received a great deal of publicity. The magnitude of PCB contamination resulting from these transformer fires has been shown to be related to the copious amount of soot which was generated during the fires (Schector, 1981). The 1980 transformer fires showed that occupational exposure to PCBs could occur in several ways - e.g. not only through dermal contact with PCB fluids during manufacture or transport, but through surface contamination following transformer explosions.

Occupational Exposure to PCBs in the Navy

Navy personnel may be occupationally exposed to hazardous levels of PCBs if they participate in cleanups of PCB spills, or if they work with transformers, gyros, capacitors, electrical power lines or noise-dampening mats or tiles that contain PCBs.

The Navy has a substantial inventory of transformers. Because many of these units were acquired before EPA environmental standards

prohibited the use of PCB dielectric fluids in transformers, many of these units contained PCBs when they were acquired or specified PCB solutions as the required dielectric fluid. Although the Navy is actively involved in conversion and reclassification of transformers, the extensive number of transformers in use has precluded complete conversion of the inventory. Personnel may thus be exposed when participating in transformer conversion, when transporting fluids for disposal, or from transformer explosions incidents, either through initial proximity to the explosion or during cleanup operations.

The potential for hazardous exposure to PCBs released during "spills" are of special concern. A "spill" is any event which causes the release of PCBs; for example, if a transformer explodes during a fire, PCBs will be released and the incident will be considered a spill. The EPA has established specific reporting requirements for PCB spills (refer to 47 CFR Part 761); for instance, if 10 (or more) pounds of PCB material is spilled, the incident must be immediately reported directly to the EPA. When PCB-containing solutions are spilled, the PCB weight is determined by multiplying the quantity of material spilled (in pounds) by the percentage of PCB present in the solution.

The EPA reporting requirements do not connote that PCB spills of less than 10 pounds are not potentially hazardous. To the contrary, the regulations governing cleanup of all spills, whether greater or less than 10 pounds of material, are considerably more stringent than those governing either background concentrations or standard occupational exposure levels. For example, the acceptable surface contamination level following cleanup has been established at 10 ug (micrograms) per 100 square centimeters of surface area (outdoor, low contact areas excepted) (43 CFR 761.125).

A similar situation is encountered in cleanup of soils. The acceptable (background) PCB contamination level has been established at 50 mg (milligrams) per kilogram of soil, however, if a spill occurs and a cleanup is undertaken, the soil must be cleaned to 10 mg per kilogram of soil (in unrestricted areas; in restricted areas, soil need only be cleaned to 25 mg per kilogram). The definition of what constitutes a "restricted" versus an "unrestricted" area appears to rest with regional EPA authorities; currently, the definitions vary widely from region to region. The EPA requirement for fill/replacement dirt is currently the most stringent standard: replacement dirt must exhibit PCB contamination levels below 1.0 mg per kilogram of soil.

To be effective, PCB cleanups must be accomplished in a timely fashion. Since PCBs are readily absorbed by many materials (concrete, wood, and plaster board, to name a few), they readily permeate many surfaces. If absorption occurs, surface cleaning will be insufficient, and removal of contaminated surfaces and even substrates may be required.

PCBs are not normally found in significant concentrations in water, since water solubilities of PCBs are comparatively low. Contamination of water reservoirs can occur, however, due to absorption of PCBs by particulate matter. Filtration methods, to remove particulate matter from water reservoirs, can be utilized to lower PCB contamination to acceptable levels.

SAMPLING METHODOLOGIES

SAMPLING METHODOLOGIES

Sampling for Occupational Exposure

Sampling methodologies for PCBs differ markedly according to the scenario encountered. For routine air sampling in occupational settings, e.g. for determining **occupational exposure**, NIOSH Method 5503 (for airborne PCBs) should be utilized. The low-flow sampling pump, 13-mm glass fiber filter, and Florisil sorbent tubes required in this NIOSH method are standard, commercially available products. It should be noted that the **only** occupational exposure standard for PCBs is airborne concentrations of PCBs (refer to the "Regulatory Standards" section of this document).

It should be noted that there is no "occupational" exposure standard, and hence no "routine" sampling methodology, for PCDFs or PCDDs. This is due to the fact that there are no commercial applications for PCDFs and PCDDs, e.g. they exist only as trace contaminants in other products or are formed as byproducts during fires or explosions involving PCBs and chlorinated benzenes.

Sampling Following PCB Spills

PCB spills require an altogether different sampling strategy. The primary concern following a spill is surface contamination, and the sampling method as well as other regulations governing PCB spills falls under the jurisdiction of the EPA and is detailed in 37 CFR 761. That document states that "visual inspection" shall be used to determine the extent of the spill, and that a "standard wipe test" will be used to verify cleanup; the minimum requirements for an appropriate wipe testing protocol are also given (the following is excerpted from 37 CFR 761.123):

"This definition consitutes the minimum requirements for an appropriate wipe testing protocol. A standard-size template (10 centimeters (cm) x 10 cm) will be used to delineate the area of cleanup; the wiping medium will be a gauze pad or glass wool of known size which has been saturated with hexane. It is important that the wipe be performed very quickly after the hexane is exposed to air. EPA strongly recommends that the gauze (or glass wool) be prepared with hexane in the laboratory and that the wiping medium be stored in sealed glass vials until it is used for the wipe test. Further, EPA requires the collection and testing of field blanks and replicates."

Sampling Following PCB Fires or Explosions

Sampling for PCBs, PCDFs, and PCDDs following a transformer fire or explosion presents yet another scenario. Since transformer fires and explosions may release PCBs, these incidents are

considered PCB "spills", and therefore cleanup must be verified by wipe sampling for surface contamination. However, there is also concern for potential exposure to PCDFs and PCDDs, which may have been generated in pyrolytic reactions during the explosion or fire. Surface wipe samples can be obtained for PCDFs and PCDDS with the same protocols used for PCBs. The additional difficulty presented is that the concentration of PCDF or PCDD will be orders of magnitude less than that of the "parent" PCB Surface sampling for PCDFs and PCDDs therefore requires the collection of wet wipes from a much larger surface area.

It should be noted than in several significant transformer incidents (Binghamton, San Francisco, Tulsa, Sante Fe) there was concern on the part of various officials that there might be residual **airborne** PCBs, PCDFs, or PCDDs following transformer incidents. In response to the first major incident (Binghamton, NY) the New York State Department of Health (NYSDH) devised sampling methodologies and obtained **customized equipment** for obtaining airborne samples. The sampling protocols devised by the NYSDH are presented below. Sampling for airborne PCDFs and PCDDs is beyond the capability of Navy personnel and, in fact, most civilian industrial hygiene facilities. The information given below on PCDF and PCDD sampling protocols will show very clearly why this is the case. It should be pointed out that there are currently no comprehensive criteria or regulations governing sampling protocols for PCDFs or PCDDs following PCB fires or explosions.

Sample Analysis

Currently, PCB air samples can be analyzed at three of the four Navy Consolidated Industrial Hygiene Laboratories (CHILs). The CHILs are accredited by the American Industrial Hygiene Association (AIHA). Navy industrial hygienists should ensure, prior to sending PCB air samples to any of the CHILs, that the particular laboratory can accommodate the hygienist's requirements. Depending on the location, and turnaround time requirements, a contract laboratory may be required. If a contract laboratory is used, the laboratory must be AIHA accredited. It is recommended that analyses be "Arochlor" specific.

Analysis of PCB wipe samples and furan and dioxin analyses are currently beyond the capabilities of the Navy CHILs, and must be performed by contract laboratories that are AIHA accredited. Analyses of furans and dioxins require the use of high resolution gas chromatography/mass spectrometry (GC/MS) methods and equipment; the chemical standards required for the analyses are some of the most toxic compounds known, and require specialized laboratory and disposal procedures. Because of these considerations, the Navy Environmental Health Center has not considered it cost-effective to develop in-house analytic capabilities for furans and dioxins. For the same reasons, only a handful of contract laboratories in the U.S. are capable, accredited, and willing to

perform furan or dioxin analyses.

Sampling Methodologies for Determining PCB, PCDF, and PCDD Contamination Levels Following Transformer Fires

The sampling methodologies which are described in this section are included to familiarize the industrial hygienist with techniques of PCB sampling, and are not intended to be used as sampling criteria. The particular protocols included below were developed to assess PCB, PCDF, and PCDD contamination levels arising from transformer fires. The protocol for PCDF and PCDD air sample collection may not be feasibly utilized by Navy personnel, since the sampling media must be specifically prepared by specialized laboratories, and the sampling devices are custom-made apparata.

The methodologies which are described below, for both surface and airborne measurements, were developed by the New York State Department of Health (NYSDH). The techniques were developed and approved for use following the occurrence of a significant transformer fire at the Binghamton, New York, State Office Building in February, 1981 (Schector, 1983). These methodologies were also used in other cities where major transformer incidents occurred - in San Francisco (Versar, 1985), Tulsa (NIOSH, 1985), and Sante Fe (Kominsky, 1986). It should be noted that the methods require non-standard products and equipment.

Air Sampling Methodology for Detection of PCBs

Air samples for PCBs may be collected using the "modified florisil stick" procedure developed by the New York State Department of Health (NYSDH).

The basic "florisil stick procedure" is a sampling method for airborne PCBs which utilizes the New York State Florisil (NYSF) stick. The NYSF stick is a glass tube measuring 9.5 inches (length) by 0.375 inches (outer diameter); it is constructed such that two compartmented sections of florisil (a proprietary magnesium silicate adsorbent developed by NYSDH) are provided in a single tube. The provision of two florisil sections allows information on migration and trapping efficiencies to be accumulated. Each florisil section contains 0.4 grams of 30/60 mesh florisil adsorbent; the two sections are separated by glass wool plugs. Plugs are also located at the front and back ends of the tube.

In the "modified" procedure adopted after the Binghamton fire, the florisil stick procedure is modified to the extent that a "trapping" mechanism is incorporated in the sampling device to remove airborne particulates: a glass fiber filter is placed

upstream of the florisil adsorbent; airborne particles are trapped in the glass fiber filter while the vapor phase is passed through and collected on the florisil. The glass fiber filter should have a pore size of 0.3 microns (micrometers) and a diameter of 47 millimeters. This modified procedure is similar to the National Institute of Occupational Safety and Health (NIOSH) Method 5503, the current NIOSH criteria for PCB air sampling (NIOSH, 1984, with 1987 Revision #1). It should be noted that the NIOSH sampling method is not validated for PCB air concentration levels of less than 0.5 ug/M^3.

Procedure - PCB Air Sampling

Each florisil tube is "spiked" by introducing 0.1 ug of p,p'-dichloro-diphenylethane (DDE) into the front end of the tube. (DDE is used as the internal standard because of its chromatographic characteristics, i.e. it is eluted in approximately the same fraction as PCBs. The concentrations of DDE and airborne PCBs can thus be analyzed simultaneously when gas chromatography-electron capture detection methods are used.)

The sampling apparatus is assembled by attaching the two-stage sampling device (37-mm glass fiber filter plus florisil adsorbent tube) to a 1.5 cubic foot-per-minute (cfm) rotary vane vacuum pump operated at 110 VAC line power. The vacuum pump should be equipped with an "in-line" calibrated rotameter and a precision flow control valve.

Air samples are collected for a 48-hour period at a flow rate of approximately 1.0 liter per minute to achieve an air volume of approximately 2880 liters.

The sampling apparatus is inspected every four hours and flow rates are recorded and adjusted as necessary. Concurrent psychrometric measurements must be taken: record the dry bulb temperature, barometric pressure and relative humidity. These data are utilized to correct the volume of air sampled to standard conditions (760 mm Hg pressure and 25^{o}C).

Ventilation and temperature conditions in the building should be representative of the conditions that are present when the building is in "normal occupancy." Building engineers must adjust the heat/ventilation/air conditioning (HVAC) system such that normal occupancy conditions are established. These conditions should be maintained for at least 72 hours prior to commencement of sampling, and for the duration of the tests. The maximum allowable volume of fresh air is 20 %.

At a minimum, a total of ten PCB air samples should be collected, at ten different locations. This sampling stategy is adopted in order to collect sufficient samples to assess the homogeneity of the air in the building.

A minimum of three field blanks must be submitted for analysis along with the PCB air samples. The blanks are required in order to determine if any background contamination has been introduced into the sampling media during handling procedures.

Surface Sampling Methodology for Detection of PCBs

Surface samples for PCBs are collected according to the "wet-wipe" protocol endorsed by the EPA; this protocol was adopted and successfully demonstrated at the several sites which experienced transformer incidents - Binghamton, San Francisco, Tulsa, and Santa Fe.

The surface wipe samples are collected using 4" X 4" gauze pads. Only gauze pads which have been specifically pre-conditioned (by Soxhlet extraction) to remove residual, or "background" PCBs may be used. Since field activities generally do not have Soxhlet extraction apparata, these gauze pads must generally be obtained from laboratories, which prepare them on request.

Procedure - PCB Wipe Samples

The sampling procedure requires that a surface area of 100 cm^2 be marked, using a template or other appropriate measuring device. Each area is then wiped thoroughly (sampling error may result from inconsistent or poor wiping) with a pre-conditioned (Soxhlet extracted) 4" X 4" gauze pad which has been wetted with pesticide-grade hexane immediately prior to wiping the area. The gauze pad should be held with stainless steel forceps; the forceps must be pre-cleaned with hexane prior to performing each wipe. The marked area must be wiped in two directions; the second direction should be a 90° angle from the first. (For example, first wipe the entire area using vertical strokes, then wipe the entire area again, using horizontal strokes.)

Each gauze pad is used to wipe only one 100 cm^2 area. After the area is wiped, the gauze pad must be sealed in a glass sample container equipped with a Teflon-lined lid.

Sampling schemes and suitable locations for PCB wipe sample collection are described in detail in the EPA's Manual for Grid Sampling of PCB Spill Sites to Verify Cleanups (EPA, 1986). Where feasible, wipe samples should be collected from nonporous internal building surfaces such as bare metal. (Porous surfaces, such as concrete, normally exhibit highly variant side-by-side sampling results. For example, the first time a wipe sample is taken from a porous surface, a value of 10 micrograms/100 cm^2 area may be obtained, while a second test, over the same area, may yield a result of 100 micrograms/100 cm^2. Such variance in results is to be expected with porous surfaces. Painted surfaces are also porous, and absorb PCBs to variable degrees).

At least one field blank should be submitted for analysis along with the PCB wipe samples. As a rule of thumb, one field blank should be submitted for every 11 PCB samples submitted.

Air Sampling Methodology for Detection of PCDFs and PCDDs

If the extent of airborne polychlorinated-dibenzofuran and polychlorinated-dibenzodioxin by-product generation is to be assessed, air samples should be collected concurrently with PCB air samples. Air samples for PCDFs and PCDDs can be collected with a high volume sampling device developed by the New York State Department of Health (NYSDH) and previously demonstrated in the Binghamton State Office Building fire. The device has been shown to be effective in collecting trace levels of airborne PCDFs and PCDDs (Smith, 1985). Currently, there are only 7 to 8 of these devices in the country (Belinky, 1990, personal communication). The entire sampling apparatus must be sent to a specialized laboratory such as the Research Triangle Laboratories (Research Triangle Park, NC) for preparation and calibration prior to each use. There is currently no published National Institute of Occupational Safety and Health (NIOSH) Method for sampling PCDFs and PCDDs.

The high volume sampler is a two-stage sampling device, which is attached to a high-flow vacuum pump. The first stage of the sampler is a glass fiber filter of 0.3 micron (micrometer) pore size and 37 mm diameter. The second stage is a cartridge containing 8 grams of silica gel adsorbent. The glass fiber filter acts to entrap particulates so that only the vapor-phase is passed through and trapped on the silica gel adsorbent. The high-flow vacuum pump must have at least a 20 liter per minute pumping capacity. Prior to using this custom-made sampler for collection, the entire sampler-and-housing must be sent to a specialized laboratory to have the silica gel adsorbent activated and the humidity checked.

Procedure - PCDF/PCDD Air Sampling

At the laboratory each silica gel cartridge is "spiked" by introducing 2.5 nanograms each of carbon-13-labeled dioxin and furan (2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran) into the front end of the cartridge. **These compounds are highly toxic.** The compounds are used as internal standards; they allow for quantification and assessment of any retention losses which may occur during sampling.

The sampling apparatus is assembled by attaching the two-stage sampling device (37-mm glass fiber filter plus silica gel tube) to a 1.5 cfm rotary vane vacuum pump operated at 110 VAC line power. The vacuum pump should be equipped with an in-line calibrated rotameter and a precision flow control valve.

Air samples are collected for a 48-hour period at a flow rate of approximately 20 liters per minute (L/min) to achieve an air volume of approximately 57.6 cubic meters.

The sampling apparatus is inspected every four hours; flow rates are recorded and adjusted as necessary. Concurrent psychrometric measurements must be taken: record the dry bulb temperature, barometric pressure and relative humidity. These data are utilized to correct the volume of air sampled to standard conditions (760 mm Hg pressure and 25^{o}C).

Ventilation and temperature conditions in the building should be representative of the conditions that are present when the building is in "normal occupancy." Building engineers must adjust the HVAC system such that normal occupancy conditions are established. These conditions should be maintained for at least 72 hours prior to commencement of sampling, and for the duration of the tests. The maximum allowable volume of fresh air is 20 %.

At a minimum, a total of six PCDF/PCDD air samples should be collected. The PCDF/PCDD air samples should be collected concurrently with PCB samples (e.g. six PCDF or PCDD samples should be collected at the same locations and during the same timeframes as six of the ten PCB air samples.) This sampling strategy allows assessment of the homogeneity of the air in the building, and correlation of PCDF/PCDD concentrations with PCB airborne concentrations.

At least one field blank should be submitted for analysis along with the PCDF/PCDD air samples. The blank is required in order to determine if any background contamination has been introduced into the sampling media during handling procedures.

Surface Sampling Methodoloy for PCDFs and PCDDs

Surface samples for PCDFs/PCDDs are collected according to the wet-wipe protocol established by the New York State Department of Health. This protocol was used to assess the contamination levels of PCDFs and PCDDs resulting from transformer fires at Binghamton, San Francisco, Tulsa, and Santa Fe.

Procedure - PCDF/PCDD Wipe Samples

The surface wipe samples are collected using 4" X 4" gauze pads, which have been pre-treated by Soxhlet extraction to remove residual PCBs. The sampling procedure differs from the wet wipe procedure for PCBs only by the amount of surface area required for sample collection and analysis.

The sampling procedure requires that a surface area of 0.25 square meters be marked, using a template or other appropriate measuring device. Each area is then wiped thoroughly with a 4" x 4"

pre-conditioned (Soxhlet extraction purified) gauze pad which is wetted with pesticide-grade hexane. The gauze pad should be held with stainless steel forceps; the forceps must be pre-cleaned with hexane prior to performing each wipe. The marked area must be wiped in two directions: the second direction should be at a 90° angle from the first. (For example, first wipe the entire area using vertical strokes, then wipe the entire area again, using horizontal strokes.)

Each gauze pad is used to wipe only one 0.250 square meter (M^2) area. After the area is wiped, the gauze pad is sealed in a glass sample container equipped with a Teflon-lined lid.

Due to detection limitations, multiple wipe samples must be collected for adequate analysis of PCDF/PCDD contamination. As defined by the NYSDH, a PCDF/PCDD wipe sample will consist of four 0.250 M^2 wipe samples, to yield a total sampled area of 1.0 M^2. In other words, for analysis purposes, four gauze pads will be treated as a single composite sample. This protocol was adopted in order to obtain analyzable levels of PCDF/PCDD contaminants.

PCDF/PCDD wipe samples are generally collected in order to verify residual contaminant levels following cleanups; in most cases, they are collected in order to establish a PCB-to-PCDF/PCDD ratio. When this is the case, they are collected in conjunction with PCB sample collection, and recommended sampling locations are areas adjacent to PCB sampling locations. As with PCBs, PCDF/PCDD wipe samples should be collected from nonporous, internal building surfaces.

Field blanks should be submitted for analysis with the PCDF/PCDD wipe samples. One field blank sample should be submitted with every PCDF/PCDD sample submitted (it should be noted that one PCDF/PCDD sample consists of four gauze pads.)

RELIABILITY OF PCB ANALYSIS

RELIABILITY OF PCB ANALYSIS

The details of laboratory analysis are not generally the purview of the industrial hygienist. In the case of PCBs, however, some familiarity with the analytical methods is desirable, for it leads to a better understanding of the difficulties associated with PCB hazard prediction. Industrial hygienists should be aware that complexities associated with the analytical procedures have led to a significant lack of reliability in reported results. For this reason, although an enormous volume of data on PCBs has been accumulated since 1970, the actual hazard associated with occupational exposure to PCBs has still not been satisfactorily determined.

The regulatory standards established by the EPA have been adopted with the full realization that toxicological data accumulated to date is by no means conclusive. Variation in sampling protocols has been one cause of the uncertainty, but the lack of reliability in PCB analysis has clearly been the most significant impediment in defining clear relationships between exposure and hazard. When the ability to quantify a material is compromised, accurate prediction of the hazard presented is also compromised.

PCB analyses are not straightforward "cook-book" operations: sophisticated detectors and methodologies are required, as are highly trained, highly specialized analysts. Interpretation of results is significantly affected both by the choice of standard and the assumptions made by the analyst; analysis has therefore been described as an "art". While some of the most basic elements of PCB analysis will be noted below, the hygienist is referred to comprehensive reviews such as the three-volume treatise PCBs and the Environment (Waid, 1986) for in-depth discussion of the methodologies and their associated complexities.

Of the several analytical methods currently utilized for PCB analysis - gas chromatography coupled with electron capture (ECGC), Hall electrolytic conductivity detection (HECD), flame ionization detection (FID), gas chromatography coupled with mass spectrometry (GC/MS), and absorption liquid solid chromatography (LSC), - each has advantages and disadvantages, and is useful for some range of sensitivity. Currently, electron-capture gas chromatography (ECGC) is considered the standard tool for PCB quantitation by many researchers, but operational difficulties are encountered even in this method (Cairns, 1986).

Fundamental to understanding the difficulties associated with PCB analysis is the realization that PCBs are multicomponent solutions which are not manufactured with precise ratios of individual chlorinated biphenyl species. For example, PCBs that are 50-60% chlorinated will contain at least 60 to 70 different compounds (Holden, 1986), and the ratios of individual components

will vary from manufacturer to manufacturer and even from batch to batch. Since the toxicity of any PCB solution is related to the degree of chlorination in the product, it is important to identify not only which PCB species are present, but how much of each type of PCB is present. Only when both of these parameters are known can some "average" value of "PCB content" be accurately reported. The need for separation of PCB solutions into individual components is the basis for utilizing chromatography; the problems associated with all PCB analyses derive from the difficulty in achieving such chromatogaphic separation.

If 60 to 70 different chlorinated species are present in a PCB solution, a "perfect" chromatogram of the solution should contain 60 to 70 different peaks; the locations of the peaks would vary according to the ratios of the particular components present in the solution, and the heights of the peaks would vary with the sensitivity of the detector employed. To obtain quantitative values for the peaks, the use of a standard would be required; the chromatogram resulting from the standard would be used to locate and assign value to the peaks appearing in the unknown, or test sample chromatogram. This standard protocol of chromatography is used to compensate for the disproportionality of detector response.

Unfortunately, there is no such standard available for PCBs. There are, instead, as many standards as there are PCB mixtures. For example, the "standard" for Arochlor 1260 is a small amount of Arochlor 1260, hopefully produced at the same factory and with the same process specifications as the commercially distributed product. Similarly, the "standard" for Arochlor 1016 is an aliquot of 1016; it will provide a chromatogram which is substantially different than that obtained for Arochlor 1260. Arolchlor 1231 will have a different profile than Arolchlor 1248, and so on.

Given an "unknown" PCB solution to analyze, which standard should be used? The answer is, the one that "looks", chromatographically, most similar to the unknown. Given five unknown samples to analyze, which standard should be used? The answer is, the five standards whose profiles most closely match the unknowns. The difficulty here is obvious. Since there are 209 possible PCB isomers, the possible variations in chromatographic peaks are almost limitless. Laboratories cannot stock an unlimited number of "standards", nor are there unlimited funds available from clients to support laboratory costs associated with repeated chromatographic trials for "best matches".

Resolution is another problem. The columns used for chromatographic separations can range in length from a few inches long to several meters long. The separation efficiency of a column is often directly related to its length, but so is the elution time. In the case where many different peaks must be separated out, very long columns (on the order of tens of meters)

may be employed, but such columns are prohibitively expensive and the elution times are exorbitantly long. Since PCB solutions are so heterogeneous, complete separations are virtually unrealizable. While "typical" PCB solutions contain 60 to 70 subspecies, the limit of chromatographic separations in most analytical laboratories is generally 20 peaks (Cairns et al, 1986).

PCB samples derived from air monitoring, wipe samples, or biological tissues present an even greater level of difficulty. Environmental and biological samples have been found to contain PCBs that only resemble initially-distributed products, e.g. they are not identical in composition to the initial products. This phenomenon is due to the fact that, although PCBs are very stable compounds, they do undergo certain reactions which cause chemical alterations: photolysis causes progressive loss of chlorination, temperature extremes and oxygen-rich environments promote conversion to furans and dioxins, biological samples may be altered by bacteriological or physiological processes, and surface wipe samples may be contaminated with other organochlorine products such as insecticide residues.

A product which may have initially contained 60 to 70 discrete subcomponents may thus, after being used in some industrial application, have over a hundred constituents. The twenty-or-so resolvable chromatographic peaks may then look substantially different than those of the pristine product. This is where the "art" of PCB analysis is applied - the degree to which the analyst can identify and "match" peaks, "throw out" peaks, and assign value to peaks is highly dependent on his or her expertise.

There have been numerous attempts to improve the reliability of PCB analysis, including the initiation of round-robin tests between qualified laboratories. A number of international intercomparison studies have been conducted by the Organization for Economic Cooperation and Development (OECD). The results of these studies, several of which are summarized briefly below, have been anything but encouraging; they have, however, served to point out the significant level of complexity in PCB analysis.

In 1969 the OECD sponsored a study in which a solution of a commercial PCB mixture (60% chlorinated) in hexane was distributed to 14 international laboratories. All of the laboratories had performed PCB analyses that were used in published scientific reports. Twelve of the 14 laboratories chose a 60% chlorinated sample of PCB as their reference standard; the results from these laboratories had a coefficient of variation of ±10.2 percent. Two of the 14 laboratories chose a 50% chlorinated sample as their reference standard; the results from these laboratories underestimated the PCB content of the solution by approximately 20 percent (Holden, 1975).

In a 1978 study, fish oil spiked with PCBs were distributed to 43 laboratories in 18 countries belonging to the International Council for Exploration of the Sea (ICES). Many analysts reported difficulty in analyzing this sample, and only 30 laboratories submitted results in the succeeding 10 month interval. Thirteen of the laboratories used the same "cleanup" technique to get rid of fats and oils (e.g. they used sulfuric acid digestion) prior to analysis; these labs reported an average PCB content of 863.15 ug/kg, with a coefficient of variation of ± 50 percent. The other laboratories, which had used different cleanup methods, reported an average PCB content of 451.40 ug/kg, with a coefficient of variation (CV) of ± 45.3 percent. Note that these CVs were calculated individually for each group, without considering data from the other group. The difference between the two averages derived by the groups is astonishing.

The last example that will be noted was an OECD-sponsored exercise conducted in 1980. This study was different from the previous ones in that the laboratories were instructed to use a common PCB standard, as well as a common method of calculation of PCB concentration. The distributed samples included a spiked oil sample and an unspiked fish oil sample (e.g. that contained "background", or environmental contamination levels of PCBs). Results for the unspiked sample gave an average PCB value of 1.07 mg/kg, with a CV of ± 31% for the 23 laboratories reporting. Results for the spiked sample gave an average PCB value of 1.93 mg/kg, with a CV of ± 21 percent (Uthe, 1982).

The variation reported in the above examples is certainly beyond the limits normally considered acceptable in analytical chemistry. In a review of the reliability of PCB analysis Holden (1986) concludes that "intercomparison exercises have confirmed the current difficulty in approaching a satisfactory level of agreement among analysts undertaking organochlorine analysis, including PCBs in environmental materials". What should be clear to the industrial hygienist is that reported values of PCB contamination or PCB exposure are "best estimate" values, not quantitative absolutes. When reviewing epidemiological or occupational exposure studies of PCBs, the context in which the data are derived should be kept in mind.

Knowledge of the difficulties associated with PCB analyses should also alert the industrial hygienist to be meticulous during PCB sample collection. Sample collections are often performed after the fact, that is, after the release of PCBs has already occurred. In these situations, it will be immensely helpful to the analyst if the type of Arochlor which was being utilized can be determined and noted. If this data is available, an appropriate standard can be chosen, and thus the PCB content can be determined more accurately.

PERSONAL PROTECTIVE EQUIPMENT

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Personal protective equipment (PPE) for PCB/Furan/Dioxin handling is currently a highly controversial subject; there is sharp disagreement by experts in the field as to what constitutes appropriate PPE. In an attempt to simplify the issue, the equipment used by several reputable hazardous waste contractors and the recommendations made by their consultants were reviewed and are presented below.

Gloves and Foot Coverings

Viton(R) rubber is the recommended material for gloves and foot coverings if it is likely that personnel will be immersed in PCB containing liquids. The ACGIH Guidelines for the Selection of Chemical Protective Clothing (ACGIH, 1987) records the breakthrough time for Viton(R) against PCBs as "greater than 24 hours"; against dichlorobenzenes it is listed as "greater than 4 hours". NIOSH has suggested that Viton(R) is the best means of protection against pure Arochlor 1254, 58% Arochlor 1254 in trichlorobenzene, and 5000 ppm Arochlor in paraffin oil (Stampfer, 1984). One problem associated with this material is its low tensile strength. It is thus highly susceptible to cuts and tears, the occurrence of which would negate any protection afforded.

Nitrile and neoprene are both recommended materials for gloves and foot coverings for PCB handlers when the possibility of immersion is not an issue. Some contractors stated that they prefer the use of nitrile due to cost considerations. The ACGIH Selection Guidelines (1987) cites the breakthrough time of PCBs through neoprene as "greater than 24 hours"; against mineral spirits the breakthrough time is recorded as "greater than 6 hours", and against dichlorobenzene it is approximately 0.5 hrs. NOISH considers both nitrile and neoprene excellent materials for protection against pure Arochlor 1254, 58% Arochlor 1254 in trichlorobenzene, and 5000 ppm Arochlor in paraffin oil (Stampfer, 1984).

Latex gloves are recommended to be worn under the protective gloves, in order to reduce the possibility of cross-contamination during protective clothing removal. It should be noted that latex rubber affords little protection against PCBs, and should never be worn as protective gloves.

Whole Body Protection

Saranex(R)-coated Tyvek(R) coveralls are appropriate for whole body protection against PCB-containing liquids. The ACGIH Selection Guidelines (1987) records the breakthrough time for Saranex(R)-coated Tyvek(R) against PCBs as "greater than 24

hours". An additional advantage of this material is the relatively low cost, making it feasible for the coveralls to be considered disposable.

A singular disadvantage of the material is that it is not resistant to mineral spirits. The ACGIH Selection Guidelines lists the breakthrough time for mineral spirits as 10 minutes. The industrial hygienist must therefore exercise caution when selecting this material: if mineral spirits are to be used as a cleaning solvent, this material should be excluded from consideration.

Teflon coveralls are also appropriate protection against PCB containing liquids; the ACGIH Selection Guidelines lists the breakthrough time for Teflon against PCBs as "greater than 24 hours". The most significant disadvantage of Teflon is the high cost: coveralls cost approximately $450 each, which effectively precludes them from being considered disposable items. Since Teflon coveralls are nondisposable, decontamination procedures must be used; this incurs additional costs.

Tyvek(R) coveralls (uncoated) offer protection against PCB contaminated dusts, and may be considered appropriate for whole body protection when PCB containing liquids are not present. An advantage of Tyvek coveralls is their low cost, and thus, disposability.

Street clothing should not be worn under protective clothing, due to the potential for carrying contamination out of controlled areas. Only cotton coveralls, which can be laundered daily, or disposable clothing may be worn under the protective clothing.

Other Protection

Shower facilities should be provided in the decontamination facility for two reasons: to control potential contamination, and to provide comfort. The requirement for showers to control potential contamination is fairly obvious, and need not be further explained. Less obvious, perhaps, is the need to consider worker morale. Hazardous waste cleanup operations are generally hot and dirty, and the requirement to work in whole body personal protective equipment often sharply decreases productivity. Anything that can be done to maintain morale at the worksite will also certainly increase productivity.

Heat stress has been a major consideration at hazardous waste cleanup sites due to the fact that use of whole body protective equipment decreases effective sweating. To address this problem, the EPA has developed guidelines for work-rest cycles, and has recommended that the cycles be implemented when personnel are required to work in whole body protective clothing. Similarly, the Army has recommended the use of Physiological Heat Expo-

sure Limits (PHEL) when personnel are required to work in MOPP suits (protective equipment similar to the coveralls described above): the PHEL charts are to be used whenever 10 degrees are added to the wet bulb globe temperature (WBGT) index. While the Navy has not yet issued specific guidelines for controlling heat stress when whole body protection is required, it is currently assessing the effectiveness of cooling vests in controlling heat stress. Regardless of which guidelines are adopted, heat stress must be considered in the selection of personal protection equipment for cleanup operations.

Respiratory Protection

Although airborne concentrations of PCBs at most spill sites have been monitored at levels below the permissible exposure limits, respiratory protection for potentially exposed personnel must still be considered. In both the NIOSH criteria document (NIOSH, 1977b) and the current NIOSH intelligence bulletin on PCBs (NIOSH, 1986) airline-supplied respirators or self-contained breathing apparata (SCBA) are recommended for <u>any detectable concentration</u> of PCB, PCDF or PCDD. The NIOSH position is based on the premise that only airline-fed respirators and SCBA are acceptable protection against carcinogens. Since PCBs have been characterized as potential carcinogens, these are the only acceptable types of respirators.

In instances where the airborne PCB concentration is known to be low, contracted PCB waste handlers have used full-face air-purifying respirators equipped with organic vapor cartridges and high efficiency filters. The Monsanto company noted that full-face respirators were selected over the half-face type, because they afforded eye protection (Monsanto, 1989, personal communication). It should be noted that when airborne concentrations of PCBs are unknown, or when they are known to be 10 times above the permissible exposure limit, higher levels of respiratory protection are required. Greater protection is also required if temperatures are significantly above standard room temperature.

FIRST AID AND EMERGENCY PROCEDURES

FIRST AID AND EMERGENCY PROCEDURES

If occupational overexposure to PCB occurs or is suspected, the worker should be referred to the cognizant Occupational Medicine Department for a situational examination.

Ingestion: Consult a physician. Do not induce vomiting or administer any oil-based laxatives.

Note to Physician: If large amounts were ingested, gastric lavage may be considered; in such cases, the risk of lavage-associated aspiration should be weighed against the risk of systemic toxicity from the ingested PCB. Generally, the amount of PCB in the ingested material should be considered, as well as the fact that PCBs have low acute toxicity.

Alternative treatments include the administration of activated charcoal, to absorb unmetabolized PCBs. The efficacy of activated charcoal is currently not known. The conventional dose of activated charcoal is 30-100 grams; an optimum dose has not been established. One dose of a saline cathartic, mixed with charcoal or administered separately, may be given.

Skin: If liquid or solid PCBs are splashed or spilled on a worker, contaminated clothing should be removed immediately and the skin washed thoroughly with soap and water*; subsequently, the patient must be referred to a physician.

Note to Physician: Hot PCBs may cause thermal burns.

Washing should include rinsing with copious amounts of running water**, then scrubbing the skin with a nongermicidal soap (make sure to wash skin folds, nail beds, and hair), followed by a rinsing with water. The process should be repeated several times.

If soap and water are not readily available, dry rags or waterless soap and rags should be used to remove as much material as possible before transporting the individual to a decontamination site. This will both reduce the quantity of PCB material that is available to be absorbed through the skin and reduce the potential for spreading the contamination to other personnel.

*The water used for decontamination may require special handling for disposal. Regional EPA authorities may have varied interpretations of federal, state or local PCB regulations. The base environmental officer should be consulted for specific disposal requirements.

**Animal studies have demonstrated that water alone will only remove about 59% of surface-applied PCBs. Multiple soap-and -water washings are necessary.

Eyes: If liquid or solid PCB material comes in contact with the eyes, the eyes should be irrigated immediately with copious amounts of running potable water for at least 15 minutes. As soon as this is accomplished the patient should be referred to a physician.

Inhalation: Remove to fresh air; refer to a physician.

Note to Physicians: In addition to systemic toxicity caused by absorption into the bloodstream, PCBs or other chlorinated hydrocarbons can generate hydrochloric acid (HCl), a respiratory irritant. HCl may be generated if arcing occurs in electrical equipment that contains PCBs or other chlorinated hydrocarbons.

General Information to Physicians: No specific antidote is known. PCBs can be absorbed through all physiological portals of entry (ingestion, skin absorption, eyes, respiratory tract). Patients may exhibit a variety of symptoms, depending on the exposure route. Patients may be monitored for the development of skin disease (chloracne), for liver disease (by liver enzyme profile), or for other possible PCB health effects (refer to toxicity profiles, presented in this report).

NAVOSH MEDICAL MONITORING REQUIREMENTS

NAVOSH MEDICAL SURVEILLANCE REQUIREMENTS

The medical surveillance protocol proposed for PCB exposures is provided in the NOHIMS MEDICAL MATRIX, 3rd Edition (NEHC Technical Manual TM89-3; Jan 1989). Polychlorinated biphenyls are listed as element 184 in the manual; the following information is exerpted from that document:

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184 POLYCHLORINATED BIPHENYLS (PCB)

STRESSOR(S) IN THIS PROGRAM:	NIOSH #	CAS #
CHLORODIPHENYL (42% CHLORINE)	TQ1356000	53469-21-9
CHLORODIPHENYL (54% CHLORINE)	TQ1360000	27323-18-8

NUMBER OF OCCUPATIONS IN THIS PROGRAM: 0
PROGRAM FREQUENCIES: ANNUAL

EXAM ELEMENT	ELEMENT GIVEN FOR:	BASE LINE	PERI ODIC	REM OVAL	OVER AGE
MEDICAL HISTORY:					
PERSONAL HISTORY OF:					
MAJOR ILLNESS OR INJURY		YES	ANNUAL	YES	10
HOSPITALIZATION OR SURGERY		YES	ANNUAL	YES	10
CANCER		YES	ANNUAL	YES	10
BACK INJURY		YES	ANNUAL	YES	10
ALCOHOL USE (SPECIFY INTAKE)		YES	ANNUAL	YES	10
SMOKING (CURRENT?, SPECIFY PACK/DAY & DURATION)		YES	ANNUAL	YES	10
HEART DISEASE, HIGH BLOOD PRESSURE, OR STROKE		YES	ANNUAL	YES	10
CURRENT MEDICATION USE (PRESCRIPTION OR OTC)		YES	ANNUAL	YES	10
ALLERGIES (INCLUDE MEDICATIONS)		YES	ANNUAL	YES	10
USE OF SEAT BELTS (ALWAYS, MOSTLY, SOME, NONE)		YES	ANNUAL	YES	10
SKIN DISEASE		YES	ANNUAL	YES	10
HEPATITIS OR JAUNDICE		YES	ANNUAL	YES	10
LIVER DISEASE		YES	ANNUAL	YES	10
WORK HISTORY OF:					
EXP TO SKIN IRRITANTS		YES	ANNUAL	YES	10
COMMENTS ON MEDICAL HISTORY:		YES	ANNUAL	YES	10
LABORATORY -					
SERUM CHEMISTRY:					
LIVER PROFILE TO INCLUDE:					
SGOT(AST), SGPT(ALT), TOT. BILIRUBIN		YES	ANNUAL	YES	10
TOT.PROTEIN ALBUMIN,		YES	ANNUAL	YES	10
ALKALINE PHOSPHATASE, LDH		YES	ANNUAL	YES	10
TRIGLYCERIDES		YES	ANNUAL	YES	10
COMMENTS ON LABORATORY RESULTS:		YES	ANNUAL	YES	10

PHYSICAL EXAMINATION:				
VITAL SIGNS	YES	ANNUAL	YES	10
SPECIAL ATTENTION IN EXAMINATION TO:				
LIVER	YES	ANNUAL	YES	10
SKIN (RASH, EROSION, ULCER, PIGMENT,	YES	ANNUAL	YES	10
ECZEMA, ETC.)	YES	ANNUAL	YES	10
OTHER APPROPRIATE EXAMINATION (SPECIFY)	YES	ANNUAL	YES	10
COMMENTS ON PHYSICAL EXAMINATION:	YES	ANNUAL	YES	10
ADVERSE HEALTH EFFECTS OF OCCUPATIONAL				
EXPOSURE?	YES	ANNUAL	YES	10
RECOMMENDATIONS:	YES	ANNUAL	YES	10

PROGRAM DESCRIPTION:

THIS PROGRAM HAS A FREQUENCY OF 12 MONTHS (ANNUAL), AND ALL TESTS ARE GIVEN ANNUALLY. WHENEVER THIS PROGRAM IS SCHEDULED FOR AN APPOINTMENT, ALL PERIODIC TESTS WILL APPEAR ON THE PROTOCOL PRINTOUT REGARDLESS OF WHEN THE APPOINTMENT IS SCHEDULED DURING THE YEAR. ALL TESTS ARE ALSO GIVEN FOR BASELINE AND REMOVAL PHYSICAL EXAMS.

REGULATORY STANDARDS

REGULATORY STANDARDS FOR PCBs

Periodically the Navy Environmental Health Center (NEHC) receives calls which indicate that there is considerable confusion about the regulatory standards which apply to specific scenarios in which PCBs are implicated. It is important for hygienists to understand that regulations governing environmental contamination levels are not synonymous with occupational exposure standards.

Occupational Exposure Standards for Airborne PCBs

The occupational exposure standards for PCBs are relatively simple. Occupational standards have been established for airborne concentrations, but not for surface contaminations. The current Occupational Safety and Health Administration (OSHA) Standards for airborne exposure to PCBs are given below:

TYPE OF HAZARD	OSHA STD. (TWA)
Airborne PCB (42% Chlorinated)	1.0 mg/M^3
Airborne PCB (54% Chlorinated)	0.5 mg/M^3

The OSHA Permissible Exposure Limits for Air Contaminants (29 CFR 1910.1000) also includes a "skin designation" for Chlorobiphenyls (42% and 54% chlorinated PCBs). The "skin designation" denotes that personal protective equipment (gloves, coveralls, goggles, etc.) should be utilized to prevent or minimize dermal absorption of the material.

Current OSHA standards governing cleanup, storage, and emergency responses to spills of hazardous materials and wastes are provided in 29 CFR 1910.120. These regulations may apply to PCBs in the case of spills. The 29 CFR 1910.120 standard can be extremely broad in scope. Small incidents can quickly mushroom into major problems, if spill or waste sites are not well defined and secured. Careful attention should be paid to this standard, including site characterization, medical surveillance, site monitoring, 40 hours of training required for cleanup participants, etc.

Environmental Standards for PCB Contamination Levels

Environmental contamination standards have been established by the EPA; they are detailed in 40 CFR 761. Some of the salient

regulations are discussed below:

Transformer Fluids

The EPA currently prohibits the use of PCB dielectric fluid in transformers, and has issued regulations governing the "conversion" of formerly contaminated units: transformers which previously contained PCB solutions must be refurbished with non-PCB fluids and reclassified as PCB-free prior to use (40 CFR Part 761).

It should be noted that PCB contaminated transformers which are drained and refilled with non-PCB fluids may still retain significant quantities of PCBs. With time, PCBs trapped in seals and other permeable materials leach out. The rate of leaching is a function of PCB solubility in the particular replacement electrolyte fluid. For example, PCBs leach more slowly into silicon-based oils than into other solvents such as chlorinated benzenes or mineral oils. For this reason, the EPA has established testing protocols requiring that, subsequent to draining and refilling with non-PCB fluids, transformers are to be operated for 90 days and then retested for PCB content. If PCB levels remain below regulated limits after 90 days, the transformer may be reclassified as a non-PCB transformer. Replacement fluids composed of silicon-based oils present a special problem: due to the slow leach rate of PCBs into silicon-based oils, the PCB content may be below the regulated levels at the 90-day point, but exceed those levels over a longer period of time.

PCB-containing solutions are normally regulated at concentrations of 50 ppm and greater: solutions with PCB concentrations between 50 and 500 ppm are defined as "PCB contaminated"; solutions with concentrations of 500 ppm and above are defined as "PCB containing" (40 CFR Part 761). There are special cases where PCB-containing solutions may be regulated at levels as low as 1.0 ppm; for example, a solution already classified as "PCB contaminated" cannot be treated as "non-PCB-contaminated" if it is merely diluted to bring the PCB levels below 50 ppm. If "PCB contaminated" solutions are diluted, the entire resultant solution must be treated as PCB contaminated. The EPA has established 2 ppm as the achievable detection level for PCBs.

Spill Cleanups and Reentry Standards

EPA regulations governing spill cleanups and reentry standards differentiate between "high contact" areas and "low contact" areas, between restricted-entry areas and non-restricted-entry areas, and between solid surfaces and soils. A synopsis of these environmental contamination level standards, which are detailed in 40 CFR 761, is given below:

SPILL CLEANUP AND RE-ENTRY STANDARDS

PCB CONTAMINATION OF:	EPA STANDARD
Outdoor electrical substations	
Contaminated solid surfaces (both impervious and non-impervious)	100 ug/100 cm^2 *
Cleanup of soils **	25 ppm, or 50 ppm (optional) and labeled
Other restricted access areas	
High contact solid surfaces	10 ug/100 cm^2 *
Low contact indoor surfaces, impervious solid surfaces	10 ug/100 cm^2 and
Low contact indoor surfaces, non-impervious surfaces (optional)	10 ug/100 cm^2 *, or 100 ug/cm^2 and encapsulated
Low contact indoor surfaces (both impervious and non-impervious)	100 ug/100 cm^2 *
Cleanup of soils **	25 ppm
Non-restricted access areas	
Furnishings, toys and easily replaced household items	Dispose of in accordance with 40 CFR 761.60.
Indoor solid surfaces and high contact outdoor solid surfaces	10 ug/100 cm^2 *
Indoor vault areas and low-contact outdoor impervious solid surfaces	10 ug/100 cm^2 *
Outdoor, low contact areas, non-impervious solid surfaces	10 ug/100 cm^2 *, or 100 ug/100 cm^2 and encapsulated
Cleanup of soils **	25 ppm

* Concentrations as measured by analysis of standard wipe samples.

** Soil is to be cleaned to the standard and excavated to at least 10 inches.

REGULATORY STANDARDS FOR PCDFs AND PCDDs

Reentry guidelines for polychlorinated-dibenzo-furans (PCDFs) and polychlorinated-dibenzo-dioxins (PCDDs) are more complicated, because they must be negotiated with the Environmental Protection Agency. The following is a summary of recommended and proposed reentry exposure guidelines for buildings contaminated with PCDDs or PCDFs as a result of Tranformer Fires, and/or pressurized releases.

Source	Recommended Concentrations[a] Air	Surface	Basis for Recommendation	Reported Lifetime Cancer Risk Estimates[b]
New York	10 pg/M^3	25 ng/M^2	c	9×10^{-8} to 2×10^{-4}
California	10 "	3 "	d	1×10^{-6} to 5×10^{-5}
New Mexico	2 "	1 "	e	$<1 \times 10^{-6}$
COT	10 "	25 "	f	$<2 \times 10^{-4}$
NAVY	2 "	*1 " **10 "	e	$<1 \times 10^{-6}$

* For areas with high potential skin contact.
** Low potential skin contact area (e.g. above 8 foot).

[a] Expressed in TCDD-equivalent units. Units are picograms per cubic meter (pg/M^3) for airborne concentrations, nanograms per square meter (ng/M^2) for surface levels.

[b] Risk corresponds to contamination from a single source--either air or surface. Risk and exposures for simultaneous exposure are additive. For example, risks reported by New York apply for exposure to 10 pg/M^3 of air only, 25 ng/M^2 of surface only, or 5 pg/M^3 of air plus 12.5 ng/M^2 of surface. Simultaneous exposure at 10 pg/M^3 of air and 25 ng/M^2 of surface implies risks twice as large as given values.

[c] Exposures based on intake of 2 pg/kg per day on workdays (0.59 pg/kg per day for life), corresponding to uncertainty factor of 500 below the No-Observable-Effects-Level (NOEL) of 1 ng/kg per day in Sprague-Dawley rats. No carcinogenicity or other toxicity observed (Kociba, 1978 and Murray, 1979). Various data sets used for cancer risk estimates. Two scenarios with and without decay.

[d] Lifetime cancer risk about 10^{-6} according to plausible assumptions, based on hepatocellular carcinomas in male B6C3F1 mice observed in gavage study at 2 doses/wk (NTP, 1982).

Both "plausible' and "worst-case" computations. Single data set for risk estimates.

[e] Lifetime cancer risk below 10^{-6} for a person spending rest of their working life in the building. Potency of TCDD isomers determined with TEFs.

[f] TCDD equivalents extrapolated from PCB guidelines with use of smallest observed ratio of PCBs to TCDD equivalents as in worst case scenario. Represents exposure to maximum of 26 pg/d, compared with recommended allowable daily intake of 650 pg/d.

Recommended allowable intake was based on safety factor of 100 below experimental NOEL for reproductive effects in rats (Murray, 1979). Dissipation/decay with 5-yr-half-life assumed.

[g] Based on all risk assessments, with primary reference to New York. For comparison, the EPA Carcinogenesis Assessment Group (CAG) risk assessment gives upper limit risk of 9.2×10^{-5} for 2 pg/kg per day on workdays--allowable daily intake from which exposure guidelines have been derived (EPA, 1981).

Like sound measurements, dioxins and furans are weighted as to the potency of the diffent isomers. There are four different weighting networks for TCDD equivalents, which are presented below. Each of the weighting networks are based upon the LD_{50s} of mice and rats. The Navy used the New Mexico State Weighting system for dioxins and furans, when they recommended the adoption of cleanup guidelines for the Naval Air Depot in Norfolk, VA in 1987. However, consultants to the Navy have been using the EPA proposed weighting system when evaluating recent releases.

2,3,7,8-TCDD EQUIVALENT WEIGHTING FACTORS

Isomers of Dioxins and Furans	NY State	FDA	*NM State	**EPA
- Mono-CDDs	0.0	0.0	0.0	0.0
- Di-CDDs	0.0	0.0	0.0	0.0
- Tri-CDDs	0.0	0.0	0.0	0.0
2,3,7,8 - TetraCDDs	1.0	1.0	1.0	1.0
Other - TetraCDDs	0.0	0.0	0.0	0.01
2,3,7,8 - PentaCDDs	1.0	0.0	0.5	0.5
Other - PentaCDDs	0.0	0.0	0.5	0.005
2,3,7,8 - Hexa-CDDs	0.03	0.02	0.02	0.04
Other - Hexa-CDDs	0.0	0.02	0.02	0.0004
2,3,7,8 - Hepta-CDDs	0.0	0.005	0.0	0.001
Other - Hepta-CDDs	0.0	0.005	0.0	0.00001
Octa-CDDs	0.0	<0.00001	0.0	0.0

	- Mono-CDF	0.0	0.0	0.0	0.0
	- Di-CDF	0.0	0.0	0.0	0.0
	- Tri-CDF	0.0	0.0	0.0	0.0
2,3,7,8	- Tetra-CDF	0.33	0.0	0.33	0.1
Other	- Tetra-CDF	0.0	0.0	0.0	0.001
2,3,7,8	- Penta-CDF	0.33	0.0	0.17	0.1
Other	- Penta-CDF	0.0	0.0	0.17	0.001
2,3,7,8	- Hexa-CDF	0.01	0.0	0.005	0.01
Other	- Hexa-CDF	0.0	0.0	0.005	0.0001
2,3,7,8	- Hepta-CDF	0.0	0.0	0.0005	0.001
Other	- Hepta-CDF	0.0	0.0	0.0005	0.00001
	Octa-CDF	0.0	0.0	0.0	0.0

* - Based upon New Mexico PCB Expert Advisory Panels recommendation on July 16, 1985, NIOSH published this in their CIB 45. (The Navy used this weighting factor when recommending the 2 pg/M^3 Dioxin equivalent for air, and 1 ng/M^2 for surface contamination in 1987).

** - EPA's Assessment and recommendation EPA/625/3-87/012 dtd March 1987.

TOXICITY OF PCBs

TOXICITY OF PCBs

PCB toxicity has been the focus of much research performed in the last two decades; an enormous volume of literature is thus currently available on PCBs. Four broad categories of research can be identified: toxicological studies, epidemiological investigations, toxicokinetic studies (including absorption and distribution rates, metabolism of PCBs, excretion phenomena) and environmental studies (which include biological monitoring of wildlife species and background exposure studies of water, air, and soil).

Toxicokinetic studies will not be reviewed; although the mechanisms of PCB interactions are of interest, this field of study is beyond the scope of this report. Review of environmental studies will also be omitted; environmental studies have proved valuable as indices of human exposure levels, but they have provided little information on the effects of such exposure.

Epidemiological and toxicological studies reflect the hazard associated with PCB exposure more directly, but both types of studies have shortcomings: epidemiological studies have often yielded inconclusive results due to the inability to quantitate initial exposure levels, due to lack of clear definition of symptoms, or to the absence of correlation with other factors, such as smoking habits or age. Animal toxicological studies have provided the most reliable correlations between exposure and effects, but have fallen short of being conclusive enough for direct extrapolation to human health hazard because of intraspecies variations in sensitivity. Another shortcoming of animal studies is that the preponderance of research has been structured around oral toxicity vice inhalation and dermal exposure toxicity. In fact, the 1956 study of Treon et al. is the only available inhalation exposure study. While several dermal exposure studies have been performed, the results have been inconclusive. Adverse effects which have been noted are generally similar to those observed in oral toxicity studies. For this reason, dermal exposure studies are not specifically reviewed in this bulletin.

Despite shortcomings, the available body of data strongly suggests that at some level, PCB exposure can be correlated with a variety of adverse health effects. Adverse effects that have been reported in either human or animal studies include dermal effects, liver damage (ranging from frank effects, such as hepatic lesions in animals, to mild enzyme induction in humans), reproductive and developmental effects, and cancer. The duration and exposure levels associated with these diverse effects have ranged from short duration/acute exposure to long duration/low level exposure.

Reviewers and regulators are faced with a formidable task when trying to assimilate all this diverse data into a coherent matrix that can be used to predict the hazard associated with discrete levels of PCB exposure. The NIOSH Criteria for a Recommended Standard (NIOSH, 1977), and the Agency for Toxic Substances and Disease Registry's recently issued Toxicological Profile for Selected PCBs (ATSDR, 1989) are documents which reflect the complexity associated with differentiating between reliable studies, extracting pertinent information from studies that reported a range of effects, and correlating intra-study data.

A comprehensive review of PCB toxicology is not possible within the scope of this report. Provided below are cursory summaries of representative toxicological and epidemiological studies; the intent is to provide the reader with a brief overview of the field.

EPIDEMIOLOGICAL STUDIES

Epidemiological studies can be roughly placed into three categories related to degree and route of exposure: the "Yusho" studies, which documented adverse symptoms occurring in populations that suffered acute exposure from ingestion incidents; occupational studies, in which personnel were exposed to PCBs through industrial accidents or through manufacturing processes with poor engineering controls - the route of exposure in these cases were from inhalation and/or dermal contact; and statistical studies, where populations exposed to low levels of environmental contamination were evaluated according to selected health indices - in these studies the route of exposure is often undefined.

"Yusho" Studies - Toxicity Related to Ingestion of PCBs

The "Yusho" studies were not only some of the earliest PCB studies, they have proved to be the most dramatic, in terms of severity of symptoms recorded. Acute effects which have been reported in populations that ingested contaminated rice bran cooking oil include dermal symptoms (acne-like lesions on the face, back, and external genitalia; hyperpigmentation of the face, nails, or gingivae; edema of the face and eyelids); hypersecretion of a cheese-like discharge from the eyes; respiratory symptoms (chronic bronchitis, sputum, persistent cough); neurological symptoms (vision problems, headache, numbness of the extremities); and more general symptoms of malaise including stomach pain, joint pain, diarrhea, irregular menstrual cycle, and general fatigue. These acute symptoms were documented in many reports (e.g. Kuratsune, 1972; Urabe, 1979).

The large populations subjected to acute toxicity in the "Yusho" incidents (approximately 1300 persons in Japan in 1968, approximately 1700 persons in Taiwan in 1979) provided the opportunity to assess long-term effects as well as acute symptoms:

Funatsu (1972) reported that in nine out of ten live births to women who had been affected by "Yusho" disease, hyperpigmentation and increased eye discharges were evident in the progeny. The symptoms reportedly disappeared over time (cited in Gaffey, 1984*).

Higuchi (1976) conducted laboratory analyses to assess blood chemistry of Yusho victims. Lowered serum cholesterol levels were reportedly found in individuals exhibiting serious symptoms; elevated serum triglyceride, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels were also reported (cited in Gaffey, 1984).

Masada (1974) and Takamatsu (1974) found that blood levels of PCBs in Yusho victims declined rapidly once ingestion of the contaminated product was terminated. Their research also indicates that five years later, the victims' blood PCB levels were only two to three times higher than those of unexposed persons (cited in Kashimoto, 1986*).

Miyata (1977) and Cheng (1981) examined the concentrations of PCBs in tissues of several patients who died within a few years after poisoning; tissue levels of PCBs were found to be higher than those of unexposed persons (cited in Kashimoto, 1986*).

*The original publications were in Japanese; the information was obtained from reviews which cite the original publications.

Two studies evaluated Yusho patients for a follow-up period of more than 16 years (Amano et al. 1984, Kuratsune, 1986). These studies reported that a statistically significant excess risk of liver cancer was found in one prefecture (e.g. when the incidence in the exposed group was compared with the incidence in the general population of that prefecture only). These results are considered only "suggestive" of cancer-associated risk, because by the 1980's it was known that the victims had also consumed polychlorinated-furans and -quaterphenyls.

Early studies of PCB toxicity, including the first "Yusho" reports, presumed that PCBs were wholly responsible for the adverse effects that were noted. However, as more data was accummulated, it was discovered that PCB solutions which were contaminated with polychlorinated-furans (PCDFs) and polychlorinated-dioxins (PCDDs) were much more toxic than "pure" PCB solutions. When the relative toxicities of PCDFs and PCDDs became apparent, the conclusions of the early studies were challenged. Subsequent re-analysis of the cooking oil ingested by "Yusho" victims proved that significant quantities of PCDFs and PCQs (polychlorinated quaternary phenyls) had, in fact, been present. Reassessment of the intake by patients showed that exposure to these compounds

was at least as great as exposure to PCBs, and laboratory tests confirmed that tissues of Yusho patients exhibited similar levels of PCBs, PCDFs and PCQs (Kimbrough, 1986).

The symptoms reported for victims of "Yusho" poisoning are the most severe health effects recorded for human exposure to PCBs. It is perhaps fortuitous that the early history of PCB health hazard included these most severe cases of exposure, since it alerted the scientific community to the need for regulatory intervention. On the other hand, there are decidedly negative aspects to having the "worst case scenario" surface first: it is possible that only the extreme symptoms associated with "Yusho disease" will be remembered, and associated with all PCB exposure. It may not be generally recognized that exposure through ingestion has been found to produce vastly different effects than exposure through other routes (inhalation and dermal contact). Nor may it be realized that the symptoms associated with Yusho disease may be more attributable to the contaminating levels of polychlorinated-furans and quaternary phenyls than to PCBs.

Occupational Studies - Toxicity Related to Inhalation or Dermal Contact

A number of epidemiological studies have been conducted of populations exposed to PCBs in occupational settings; in these cases PCB exposure has been through inhalation or dermal contact. Although dermal contact is thought to contribute significantly to occupational exposure, air monitoring has generally been the only measurement of PCB exposure, thus the relative contributions of dermal and inhalation exposure in occupational settings has not been discerned (Wolff 1985).

Symptoms and potential effects which have been evaluated in the occupational studies include skin rashes and chloracne, abnormal liver function (as monitored by enzyme activity), changes in fat metabolism, changes in blood chemistry and blood pressure, and carcinogenicity. Of these, the only adverse effect that has been definitively correlated with PCB toxicity is dermatitis (skin rash, burning eyes, burning skin), and a particular type of skin lesion called "chloracne".

Dermal Effects

Chloracne is characterized by the appearance of acne-like dermal lesions; the lesions have often been located on the face and neck, the back, and less often, on external genitalia. Chloracne was associated with PCB exposure in an early study: in a 1954 study, 7 of 14 workers who had been exposed to PCBs were reported to have developed chloracne. The breathing zone levels of PCB had been monitored, and were reported to be on the order of 0.1 mg/M3 (Meigs et al., 1954).

Chloracne and skin rash have since been correlated with PCB exposure in a number of studies (Ouw et.al., 1976; Fischbein et.al., 1979, 1982, 1985; Baker et.al., 1980; Smith et.al. 1981a,b, 1982; Kimbrough, 1987a). In many of the studies, attempts were made to correlate the occurrence of chloracne with a specific level of exposure, as monitored by blood serum levels of PCBs. The results were inconclusive, even though several studies were of rather large populations. For example, Fischbein et.al. (1979) evaluated 289 capacitor manufacturing workers; in this study a statistical difference was found between the PCB plasma concentrations of males that exhibited skin abnormalities and those that did not, but only when the concentrations of highly chlorinated PCBs were considered. There was no significant difference in the levels of lower-chlorinated PCBs. These findings can be compared with those of Smith et.al. (1982), who evaluated 324 exposed workers in capacitor manufacturing and transformer repair operations; this study reportedly found no chloracne among this group of workers, although skin rash was noted in some individuals. The blood serum PCB levels were found to range from 38 to 356 ug/kg, and a correlation was found between skin rash and high serum levels of highly chlorinated PCBs.

Liver Effects

Abnormalities of liver-related enzymes have been evaluated in numerous epidemiological studies (Ouw et al. 1976; Alvares et al. 1977; Fischbein et al. 1979, 1985; Baker et al. 1980; Smith et al. 1981a,b,c; Maroni et al. 1981a, Emmett 1985; Kreiss 1985). In those studies which found some statistical differences between exposed workers and nonexposed populations, the most common finding was elevation of serum enzymes such as SGOT and SGPT.

Most reviewers note that these elevations were subclinical, e.g. that they were not correlated with any actual liver dysfunction. SGOT and SGPT activity levels are generally considered indicators of possible liver microsomal enzyme induction or possible hepatocellular damage, but in those studies where elevated enzyme activity was found, no liver dysfunction was observed. A conclusion stated in the ASTDR report reflects the conclusions drawn by most reviewers: "These increases show generally inconsistent patterns, may be nonspecific, may be within the normal population range, and have not been shown to be associated with hepatic dysfunction" (ATSDR, 1989).

The search for indications of hepatic effects in humans is warranted because liver damage is a consistent finding in animal toxicity studies.

Changes in Fat Metabolism, Blood Chemistry, and Health Indices

The effect of PCBs on fat metabolism has been evaluated in several studies (Baumgardner 1973; Baker 1982; Smith 1982; Kreiss

1981;, Baker 1980; Chase 1982). Evaluations were based on differences in cholesterol levels, and/or differences in triglycerides, phospholipids or beta-lipoprotein levels. The results have proved to be so inconsistent that no correlation between fat metabolism and PCB exposure can be established. While some studies reported increases in serum cholesterol, others reported negative findings; a sufficient number of studies found small but statistically significant increases in triglyceride levels that a correlation is "suggested", although not proven (Gaffey, 1984).

Only a few studies have included assessment of blood chemistry (Baumgardner 1973; Fischbein, 1979; Baker 1980; Maroni, 1981a). No significant alterations to blood chemistry were found.

A number of epidemiological studies have attempted to evaluate the degree to which PCB exposure has increased the incidence of illness in a population. By comparing the incidence of a variety of symptoms and illnesses in exposed and non-exposed populations, it was hoped that statistically significant differences in overall health could be detected. Some of the parameters which have been evaluated in these types of studies include the incidence of fever, weight loss, anorexia and fatigue (Baker, 1980); the incidence of neurological symptoms such as headache or numbness (Murai, 1971; Fischbein, 1979); gastrointestinal effects such as diarrhea and abdominal pain (Fischbein, 1979, Maroni et al. 1981b); and a variety of other indicators of adverse health effects such as the number of miscarriages and stillbirths in the populations (Kreiss, 1981).

As no guidelines exist to govern the choice of health indices, diverse indicators have been chosen in these studies and therefore, diverse results have been reported. In those studies which found any statistically significant differences, the reported differences were small. The conclusion of Smith (1982) that "no studies to date have shown that occupational exposure to PCBs is associated with adverse health outcome [other than chloracne]" is shared by many reviewers.

Carcinogenic Effects

There have been few occupational studies which have evaluated carcinogenic effects. This may be partly due to absence of any noticeable appearance of cancers in acutely exposed populations (such as the Yusho groups) and partly due to the long latency periods associated with many cancers.

Bahn et al. (1976, 1977) examined a group of 92 persons, 41 of which were refinery plant employees and 31 of which were defined as "research and development" employees. Malignant melanoma was found in three workers and pancreatic cancer was found in two employees. The results are considered inconclusive for several reasons: the exposure levels were not quantified,

the number of cases observed was small, and the number of cancers found were only statistically significant because the calculations were based on the overall cancer rates of the U.S. population, and not on the cancer rate of the area considered (which is higher than the U.S. rate) (NIOSH 1977b).

Brown and Jones (1981) studied 2,567 workers that had been employed for at least three months in capacitor plants. This was a retrospective mortality study, and at least half of the cohort had a latency period of twenty or more years. Mortality from all causes and all cancers was found to be lower than expected, but a statistically significant excess of rectal cancer was reported. Excess mortality from liver cancer (3 observed deaths versus 1.19 expected) was also reported, but it was also found to be inversely related to duration and latency of exposure of the subjects. The excesses are not statistically significant (ATSDR, 1989) if compared to the rates of the local area instead of with the U.S. population rates.

Gustavsson et al. (1986) studied 142 male capacitor-manufacturing workers which had been exposed to PCBs for an average of 6.5 years. Seven cancers were found, but this number was not a statistical excess when compared to national statistics. The authors concluded that their data did not indicate any excess mortality or cancer incidence among PCB workers.

An occupational study by Bertazzi et al. (1987) provides suggestive evidence for carcinogenicity of PCBs by the inhalation route. This retrospective mortality study evaluated 544 male workers and 1156 female workers who had been employed in a capacitor-manufacturing plant between 1946 and 1982. Overall mortality rates for males were not significantly different from either national or local rates, but mortality from all cancers was significantly higher than the national and local rates. Overall mortality rates for women were not statistically different from national rates, but were higher than local rates. Mortality from all cancers exhibited the same pattern: cancer mortalities were not statistically different from the national rates, but were higher than the local rates.

Available epidemiological data has not been sufficient to indicate a consistent carcinogenic effect from PCB exposure. Since the studies by Brown and Bertazzi have yielded "suggestive" evidence, and there was suggestive evidence of carcinogenicity in some of the Yusho studies (e.g. Kuratsune, 1986) the EPA has concluded that the evidence for carcinogenicity in humans is "inadequate but suggestive" (EPA, 1988b).

The EPA has used animal toxicity studies as the basis of a quantitative carcinogenicity risk assessment for PCBs (EPA, 1988a). The dietary PCB level which was found to produce carcinogenic effects in rats was converted from 100 ppm (reported level) to an intake value of 5 mg/kg/day by assuming that a rat

consumes food equal to 5% of its body weight per day. This intake value, or dosage, was then converted to a time weighted average dosage of 3.45 mg/kg/day by taking into account the overal dosages in the study (the rats were fed 100 ppm for 16 months, 50 ppm for 8 months, and 0 ppm for the last 5 months). The rat dosage was then converted to an "equivalent" human dose; on the basis of relative body surface areas, the equivalent human dose was calculated to be 0.59 mg/kg/day. Since there is no information regarding which constituents of a PCB solution might be carcinogenic, the EPA potency estimate applies to all PCB mixtures (EPA, 1988a).

Reproductive and Developmental Toxicity

No data on human reproductive effects is available in current literature (ATSDR, 1989).

Developmental toxicity was evaluated in a study by Taylor et al. (1984). Mean birth weights and mean gestational ages of infants born to women who had worked in high and low exposure areas in two capacitor-manufacturing plants were compared. Although statiscally significant differences were reported, the differences were rather small: gestational age was 6.6 days less, mean birth weight was 153 grams less. The results of this study are considered inconclusive because a number of factors were not considered (smoking and alcohol consumption, previous history of low birth weight, etc.)

Other studies have reported slight developmental effects in infants who were born to mothers that were consumers of contaminated fish (Fein et al. 1984, Jacobson et al. 1985). Effects that were noted included slight differences in birth weight, head circumference, gestational age, or neonatal behavior. However, these studies fell short of establishing conclusive effects, because a number of important parameters were omitted, including documentation of exposure to other chemicals. Additionally, significant inconsistencies between the studies cast doubt on the reliability of the data. Developmental toxicity studies in humans have therefore been considered suggestive but not conclusive.

ANIMAL STUDIES

The weight of evidence for PCB toxicity has come from animal studies. Since doses can be controlled in animal studies, more reliable correlations between exposure and effects can be made. A major shortcoming of animal toxicity research has been the preponderance of oral toxicity studies. No doubt this is due to the inherent complexities associated with maintaining airborne concentrations of PCBs for long periods of time. While doses of PCBs can be administered orally with ease, and dermal application is also easily accomplished, maintaining a constant airborne

level for inhalation is no simple task. This is unfortunate, since human occupational exposure is most commonly through inhalation routes.

Dermal Effects

Oral toxicity studies in animals have confirmed that cutaneous tissues are target organs of PCB action. Symptoms exhibited in several studies of rhesus monkies (Allen and Norback 1973, Allen 1975, Barsotti et al. 1976, Thomas and Hinsdill 1978, Becker et al. 1979, Allen et al. 1979, McNulty et al. 1980) have included facial edema, purulent discharges from the eyes, chloracne and alopecia (loss of hair on the head). These animal data are generally consistent with the cutaneous effects observed in occupationally exposed humans.

No inhalation studies have been performed on animals to evaluate dermal effects.

Liver Effects

Numerous oral toxicity studies have established that the liver is a target organ of PCBs in animals (Litterest et al. 1972, Kimbrough et al. 1972, 1975, Bruckner et al. 1974, Allen 1975, Barsotti et al. 1976, NCI 1978, Biocca et al. 1981, Carter 1985, Norback and Weltman 1985). The parameters which have been used to evaluate hepatic effects have included histological evaluation (degenerative lesions, fatty tissue degeneration, areas of necrosis, enlarged hepatocytes), relative liver weights, and microsomal hydroxylase, microsomal nitroreductase and demethylase activities.

Litterman et al. (1972) reported that increased nitroreductase and demethylase activity occurred at approximately 5 ppm, and relative increases in liver weight occurred at approximately 500 ppm, in Osborne-Mendel rats exposed to Aroclors 1260, 1254, 1248, or 1242 at concentration of 0, 0.5, 5.0, or 500 ppm for 4 weeks.

In a study of 22 rhesus monkeys fed diets containing Aroclor 1248, autopsies on two female monkeys that died after being fed Aroclor 1248 (one for 3 days, the other for 310 days at doses of 2.5 ppm and 5.0 ppm, respectively) revealed areas of necrosis, enlarged hepatocytes, and lipid droplets (Barsotti et al. 1976).

Chu et al. (1977) reported that fatty degeneration in the liver was observed in rats exposed to ≥20 ppm Aroclor 1254 or 1260 for 20 days. Frank histological effects were also reported by Kimbrough et al. (1972), in rats exposed to ≥20 ppm of 54% and 60% chlorinated PCBs for 8 months, and by Koller (1977), in mice exposed to 37.5 ppm Arochlor 1254 for 6 months. It is interesting to note that the Koller study found that mice exposed to one-tenth the dose (3.75 ppm Aroclor 1254) for six months exhibited

no histological effects.

Three studies which examined hepatic effects associated with long-duration feeding exposures found no degenerative lesions, but reported finding pre-neoplastic and nonproliferative liver lesions (NCI 1978, Morgan et al. 1981, Ward 1985). In these chronic feeding studies, rats were exposed to 25 to 100 ppm Aroclor 1254 for two years.

In addition to the oral toxicity studies, one inhalation study has shown that hepato-toxicity can be linked to airborne levels of more highly chlorinated PCBs: the Treon et al. study (1956) reported finding degenerative liver lesions in rats, mice, rabbits, guinea pigs, and cats that were exposed to Aroclor 1254 (54% chlorinated PCB) at vapor levels of 1.5 mg/M3 for 7 hr/day, 5 days/week for 213 days. Other groups of these animals did not exhibit histologic degeneration in liver cells when exposed to a lower-chlorinated PCB, Aroclor 1242 (42% chlorinated PCB) at vapor levels of 1.9 mg/M3 for the same intervals.

Dermal exposure has also been correlated with hepatological effects in at least two studies. In the first study (Vos and Beems 1971), Arochlor 1260 was applied to the shaved backs of groups of female rabbits; the Arochlor was in an isopropanol vehicle, and was applied at a dose of 118mg/day for 5 days/week for 38 days. In the second study (Vos and Notenboom-Ram 1972), the dose was 120 mg/day for 28 days. Both studies reported finding histological effects, including centrolobular degeneration, liver cell atrophy, enlarged nuclei, and loss of glycogen.

Immunological Effects

Some evidence of immunosuppression has been observed in oral toxicity studies in mice, guinea pigs, and rhesus monkeys. Indications of immune system effects have been monitored by lowered antibody response to sheep red blood cells (Thomas and Hinsdill 1978), susceptibility to infection (Barsotti et al 1976), and lowered levels of circulating leukocytes and lymphocytes (Vos and Generen 1973).

Thymus atrophy, as well as significantly lowered tetanus autotoxin titers, and lowered levels of circulating leukocytes and lymphocytes, were reported in female guinea pigs that were kept on diets that contained 50 ppm doses of Aroclor 1260 for 6 weeks (Vos and van Generen 1973). A decrease in thymus weight was observed in mice that were maintained on a diet which contained 10 ppm of a hexachlorinated PCB for 5 weeks (Biocca et al. 1981). Splenic, thymic, and lymph node atrophy have also been observed in rats (Allen et al. 1975, Parkinson et al. 1983).

No inhalation studies have been performed to evaluate immunosuppression in animals. Since immune system effects have not been demonstrated in human exposure studies, the significance of

immune system effects in animals from oral exposure routes is not clear.

Carcinogenicity

A number of oral toxicity studies have been performed to evaluate carcinogenic effects (Kimbrough et al. 1972, 1975, Kimbrough and Linder 1974, Ito 1974, NCI 1978, Schaeffer et al. 1984, Norback and Weltman 1985). Rats and mice were the only animals used in these studies. Where statistically significant carcinogenic effects were found, the liver was always implicated: reported effects include liver nodules, evidence of neoplastic cells in the liver, hepatocellular carcinomas and adenomas. Cancers other than hepatic have also been reported (lymphomas, leukemias, adenocarcinomas in the stomach and jejunum). These have been exhibited much less frequently, and in several cases the incidence has not been large enough to be significant.

In a 1972 study, Kimbrough et al. fed groups of male and female rats (10 rats per sex per dose) with Aroclor 1254 or 1260 at doses of 1, 100, 500, or 1000 ppm for a year. The rats were then sacrificed and examined. No histological evidence of carcinogenicity was found; neoplastic nodules or hepatocellular carcinomas were not evident.

In another Kimbrough et al. study (1975) weanling Sherman rats were fed with diets containing 0 or 100 ppm Aroclor 1260. The rats were killed at 23 months of age. The treated rats were found to have significantly reduced body weights, and almost all treated rats exhibited liver nodules, although only one rat was found to have gross abnormalities of the liver. Hepatic carcinomas were found in 0.58% of the untreated rats (1/173) and in 14% of the treated rats (26/184). The neoplastic nodules were not found in any of the untreated rats, and were found in 144/184 of the treated rats. The conclusion that can be drawn from these two studies is that hepatic carcinomas may only occur when PCB exposure is of long duration. This study was once used by the EPA as the basis for the carcinogenicity risk assessment for PCBs (EPA, 1985a).

A more recent study, by Norback and Weltman (1985) evaluated carcinogenicity in two groups of Sprague-Dawley rats. Seventy male rats and seventy female rats were maintained on a diet containing Aroclor 1260 for 24 months. The concentration of Aroclor was kept at 100 ppm for 16 months, then at 50 ppm for 8 months, and was eliminated from the diets for a 5 month period. Some rats were examined in the 18th month; in the treated rats, 95% of the 47 females and 15% of the 46 males were found to have hepatocellular neoplasms; in the untreated rats, no hepatological effects were found in the males (0/32), and only 1 female (1/49) was found to have a single neoplastic nodule.

Another important parameter was monitored in the Norback and Weltman study: the progression of the cellular neoplasms from becoming the foci of cell alteration (at 3 months), to neoplastic nodules (at 12 months), to trabecular carcinomas (at 15 months), and to adenocarcinomas (24 months). The observation of such progression is the morphologic criteria for malignancy, hence, this study establishes that malignancy is a toxic effect of PCB exposure. For this reason the EPA recently selected the Norback and Weltman study as the basis for carcinogenic risk assessment for PCBs (EPA 1988a, b). It should be noted, however, that the authors were careful to point out that the tumors which were observed in this study were relatively unaggressive, and did not metastasize to other organs or invade blood vessels. Furthermore, the tumors did not affect mortality.

Malignancy was not so clearly indicated in a study conducted by the National Cancer Institute (NCI, 1978). When male and female groups of Fischer rats were exposed to 0, 25, 50, or 100 ppm Arochor 1254 (exposure was for 104 to 105 weeks, 24 rats per sex per dose were evaluated) hepatocellular adenomas and carcinomas were found in the treated rats and not in the untreated controls, but the tumor incidences were not sufficiently large to be significant. Other findings were also less than definitive: Significant dose-related reduction in survival was only found among treated males (e.g. survival reduction was not found among treated females). The combined incidences of lymphomas and leukemias in all treated males was found to be significant when compared to all untreated males, but if the incidence of lymphomas and leukemias for each dose group was compared with the controls for that dose group, the difference was not great enough to be significant. The NCI concluded that the high incidence of hepatocellular lesions in the rats (both male and female) was related to treatment, but that carcinogenicity was not established in this bioassay.

It is important to note that no inhalation studies have been performed which evaluated carcinogenic effects in animals. While orally administered doses of PCBs have been shown to effect carcinogenic responses, no studies have shown that the same responses would be effected by inhalation exposure. In the absence of such data, oral toxicity studies are used as the basis to predict human exposure effects.

Reproductive Toxicity

Oral toxicity studies have established that reproductive toxicity is associated with PCB exposure. Animal species exhibit varying sensitivities to the exposure, with minks exhibiting much more sensitivity than rats. Monkeys have also been shown to be very sensitive, however, the effect of contaminating PCDFs in the studies lends some ambiguity to the significance of the results.

Linder et al. (1974) recorded reduced litter sizes in rats that were fed sufficiently high doses of PCBs. In this study groups of rats were exposed to 0, 1, 5, 20, 100, or 500 ppm Aroclor 1254. Reduced litter sizes were observed at the 20 ppm doses and larger doses. Both one- and two-generation reproduction studies were performed.

Reproductive failure was recorded in mink that had been maintained on diets that provided 15 ppm Aroclor 1254 for 4 months prior to mating and during gestation. Groups of rats were maintained on diets that contained 0, 1, 5, or 15 ppm Aroclor 1254; dose-related reproduction impairment was observed at 5 ppm (fewer females whelped, and litter sizes were reduced). Total inhibition of reproduction was observed at 15 ppm; at this dose the PCB treatment was lethal to fetuses (Aulerich and Ringer 1977).

Barsotti et al. (1976) and Allen et al. (1979) evaluated reproductive toxicity in rhesus monkeys. Monkeys were fed diets containing 2.5 or 5.0 ppm Aroclor 1248 for 18 months. At the lower dose level, early abortions and fetal resorptions were observed, but some live births also occurred. At the higher dose level there was almost complete inhibition of reproduction. An unfortunate aspect of this research was that the PCBs used were found to be contaminated with approximately 1.7 ppm PCDFs, thus the results are somewhat compromised, since PCDFs may have contributed to the toxicity.

As in the case of so many other effects, no inhalation studies have been performed to evaluate reproductive effects in animals that might occur in response to exposure by this route.

Developmental Toxicity

While reproductive toxicity from oral exposure has been well documented in animal studies, developmental toxicity is less obvious.

Collins and Capen (1980a) found ultrastructural lesions in thyroid follicular cells and reduced levels of thyroid hormone in neonates and weanlings of rats fed 50 ppm and 500 ppm Arochlor 1254 during gestation and lactation. Statistically significant decreases in pup body weight were not observed at 7 or 14 days, but were observed in 21-day-old pups.

Villenueve et al. (1971) found that doses of 12.5 mg/kg/day and greater, administered during gestation, produced fetotoxic effects in rabbits. Doses of 10 mg/kg/day did not produce fetotoxic effects.

Haake et al. (1987) reported that no cleft palate was observed in mice treated with Arochlor 1254 during pregnancy. 244 mg/kg of the PCB was administered on day 9 of gestation. (Cleft

palate was first implicated as a possible reproductive effect in one of the "Yusho" follow-up studies; although the incidence was not sufficiently high to be statistically significant, the low number of subjects affected the results; cleft palate is therefore considered a potential indicator of reproductive toxicity).

Barsotti and Van Miller (1984) evaluated offspring of monkeys that were fed diets containing Arochlor 1016 at doses of 0, 0.25, or 1.00 ppm for 7 months prior to mating and during pregnancy. All females conceived and delivered viable offspring. Mean birth weight in the 1.0-ppm group was found to be significantly less than controls, but head circumference and length were unaffected.

In the monkey studies conducted by Allen and Barsotti (Allen and Barsotti 1976, Allen et al. 1979, 1980) higher doses were administered (2.5 or 5.0 ppm) and Aroclor 1248 was used. Fetotoxic effects were more pronounced, and included early resorption, stillbirths, and reduced birth weights.

Lethality

In the only animal inhalation study of PCBs, Treon et al. (1956) showed that near saturation vapor concentrations of Aroclor 1242 was not lethal for rats, mice, rabbits, guinea pigs, or cats. It should be noted that near-saturation concentrations of PCBs are not easily obtained; it was necessary to heat the Arochlor solution to achieve these concentrations (8.6 mg/M3). The animals received an exposure level of 8.6 mg/M3 for 7h/day, 5 days/week for 24 days. This study is significant because inhalation exposure is the route by which most human occupational exposures occur. The conditions required to achieve near-saturation concentrations in laboratory settings suggest that these conditions are hardly ever encountered in industrial settings. Only in the case where large vats of Aroclors were continually heated could such conditions be approached.

Oral toxicity studies have been used as the basis for establishing lethality doses. This is not surprising, since much higher "exposure levels" can be achieved orally. Whereas the doses administered in inhalation experiments are dependent on vapor pressure limitations, an extensive range of doses can be administered through oral routes.

Lethal doses (LD_{50}s) have been established for a number of PCBs in various animal species. Animal species have exhibited markedly different sensitivities to Aroclors. For example, single-dose oral LD_{50}s for mink have been reported to be as low as 750 mg/kg, when Aroclor 1221 (21% chlorinated) was used (Aulerich and Ringer, 1977). At the other end of the range, single-dose oral LD_{50}s for rats have been reported to be as high as 1,010 mg/kg, when Aroclor 1254 (54% chlorinated) was used (Garthoff et al. 1981). This is clearly due to intraspecies

variation, since more highly chlorinated PCBs are generally more toxic than lower-chlorinated PCBs.

LD_{50}s from dietary exposure have also been determined for a number of animal species. LD_{50}s in mink were determined to be 79-84 ppm in a study where groups of these animals were given either 79-84 ppm or 47-49 ppm Aroclor 1254 for 28 days followed by a 7-day withdrawal period (Hornshaw et al. 1986). Based on average mink food consumption, 79-84 ppm is equivalent to an LD_{50} of 8.8 mg/kg/day (ATSDR, 1989).

Decreased Longevity

Decreased survival has also been evaluated only by oral toxicity research, since the inhalation study of Treon et al. (1956) did not indicate decreased longevity; although decreased survival from oral exposure has been reported in some studies, it has not been a universal finding. In a study conducted by the NCI, groups of 24 male rats were fed diets that contained 0, 25, 50, or 100 ppm Aroclor 1254 for 104 weeks. Dose-related decreased survival was found to be 92, 83, 58, and 46%, respectively (NCI, 1978). However, in other studies where rats were given 100 ppm of a 60% chlorinated PCB for equivalent periods of time, either no decreased survival was found (Norback and Weltman, 1985) or an increase in survival was found (Schaeffer et al. 1984).

Since none of the research on human occupational exposure has indicated decreased longevity, and considerable ambiguity is reflected in the findings of animal oral toxicity studies, decreased longevity is not an established effect of PCB exposure.

TOXICITY OF POLYCHLORINATED DIBENZO-FURANS AND POLYCHLORINATED DIBENZO-p-DIOXINS

TOXICITY OF PCDFs and PCDDs

Polychlorinated-dibenzo furans (PCDFs) and polychlorinated-dibenzo-p-dioxins (PCDDs) are some of the most toxic synthetic chemicals known (Buser, 1985). Unlike PCBs, which have wide industrial applicability, PCDFs and PCDDs have no commercial applications. Both of these compounds arise as trace byproducts in the processes which produce other chlorinated products such as chlorobenzenes, trichlorophenols, and PCBs. The public was largely unaware of their existence until about 1978 or 1979. The scientific community was alerted to their existence and to the health hazard they presented only a few years earlier. Isolated industrial disasters at chemical plants and waste sites and the use of Agent Orange in the Vietnam war led to their discovery.

In 1970 Vos et al. reported that PCDFs were present as by-products, at a parts per million (ppm) level, in both West German and French PCB products (all were 60% chlorinated products). An interesting phenomena which had been observed was that the various PCB solutions exhibited pronounced differences in toxicity. Subsequent research showed that the toxic effects of the PCB products were proportional to the level of PCDFs present; this suggested that PCDFs were extremely more toxic than the PCBs themselves, for they constituted an extremely small percentage of the product.

PCDD compounds were similarly found to be the most toxic component of certain herbicides. The herbicide 2,3,5-T (a trichloro-phenoxy acid) was widely used for deforestation in the 1960's and 1970's. One of the advantages of 2,3,5-T was that it degraded rapidly in soil and thus was considered to pose no hazard to the environment (the half-life of dioxins is on the order of a year or less). Until herbicide sprayers suffered adverse health effects - notably, the U.S. troops in Vietnam who were required to dispense enormous amounts of the herbicide Agent Orange - the presence and significance of PCDD contamination was not well known.

PCDFs and PCDDs are more toxic than PCBs by several orders of magnitude. When reviewing epidemiological and toxicological data the reader should note that airborne concentrations are expressed in terms of <u>parts per billion</u> (ppb) or <u>parts per trillion</u> (ppt) and that oral doses are expressed in terms of <u>micrograms</u> or <u>tenths of micrograms</u> per kilogram body weight (whereas PCB data is reported in terms of several hundred parts per million for airborne concentrations and milligrams per kilogram of body weight for oral doses).

The PCDFs and PCDDs found in PCBs and other polychlorinated aromatic compounds are complex mixtures composed of many different isomers. Since the parent dibenzo-furan and dibenzo-dioxin molecules have eight positions available for chlorine substitution, 135 PCDF isomers and 75 PCDD isomers are possible. It is essential to realize that there are pronounced differences in toxicity between isomers. Toxicity has been found to depend both on the number and position of the chlorine substituents of a congener (Poland et al. 1976, McConnell et al. 1978). It is highest for the tetra-, penta- and hexachloro compounds, and highest for isomers fully chlorinated at the lateral positions (the 2-, 3-, 7-, and 8- positions). The most hazardous compounds are thus the so-called 2,3,7,8-substituted isomers. There are 7 such isomers in the PCDF series and 5 in the PCDD series. Among these, the most toxic compound is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD or TCDD); it also has been shown to have the greatest carcinogenic potential (Rappe and Buser, 1980).

Toxicity data for PCDFs and PCDDs is derived primarily from PCDD toxicological studies, and especially from studies of 2,3,7,8-TCDD. Data derived from PCDD research is considered representative of the toxicity of both types of compounds since it has been demonstrated that PCDFs and PCDDs that are chlorinated to the same degree and in the same configuration exhibit similar toxicity (Poland et al. 1977, 1982).

Potential sources of human exposure to PCDFs and PCDDs which have been identified include polychlorinated aromatic production processes (especially hexachlorophene production); production or use of halogenated phenols in wood preservatives, slimacides, bacteriocides and cutting fluids; PCB production processes; use of PCBs in heat-transfer systems; and incineration, storage, or repair of transformers and capacitors containing PCBs and/or other halogenated aromatic compounds. The production of PCDFs and PCDDs in tranformer fires is of special concern, since a great number of transformers in current use contain PCBs. The soot from a large transformer fire which occurred at the Binghamton, New York, State Office Building in 1981 was found to contain significant amounts of PCDFs and PCDDs (Schector and Tiernan 1985). Such production of PCDFs and PCDDs during fires and explosions involving PCB-filled equipment has been demonstrated in a number of instances (Rappe et al. 1985, O'Keefe et al. 1985, Milby et al. 1985).

Buser (1978, 1979) examined the chemical reactions that lead to the formation of PCDFs and PCDDs during pyrolysis of chlorobenzenes. His data provided evidence that conditions achieved in transformer fires and explosions are conducive to PCDF and PCDD generation.

HUMAN EXPOSURES TO PCDFs AND PCDDs

The only published account of human exposure to pure PCDD is a report of three scientists who were exposed at two government laboratories in the U.K. Two of the scientists developed chloracne, while the third developed dioxin-related adverse symptoms without chloracne. Delayed symptoms were exhibited two years after the exposure and included personality changes, neurological disturbances, and hirsutism (excess hairyness) (Oliver 1975).

All other recorded human exposures to PCDFs and PCDDs have been through exposures to mixtures of other chemicals which were contaminated with these compounds. Since the symptoms observed are due to mixed exposures, it may never be possible to determine the toxicity of these compounds in humans. Both acute exposures and chronic exposures to human populations have occurred. Acute exposures have been caused by industrial accidents at chemical plants producing chlorophenol and chlorophene products; chronic exposures have resulted from herbicide spraying operations and proximity to waste sites. A third type of exposure is associated with proximity to transformer fires or explosions. This type of exposure is difficult to categorize because the extent of exposure is related both to proximity and exposure time at the initial event and to exposure resulting from contact with residues generated during the event.

Epidemiological studies of PCDF and PCDD exposed populations have several shortcomings: the initial exposure doses are unknown, the amount of exposure to other toxic materials can often not be determined, and many of the symptoms exhibited or professed are not unique to toxic exposure (the exception is chloracne).

Industrial Accidents - Acute Exposures

In the last four decades a number of PCDF/PCDD exposures have occurred as a result of industrial accidents at chemical plants in Europe or the U.S. About 18 distinct industrial industrial exposure incidents have been recorded, including:

	Persons Exposed
1949 - Monsanto (Nitro, West Virginia)	250
1953 - BASF (Luwigshafen, West Germany)	75
1956 - Rhone Poulenc (Grenoble, France)	?
1963 - NV Philips (Amsterdam, the Netherlands)	106
1964 - Dow Chemical (Midland, Michigan)	61
1965-1969 - Spolana (Prague, Czechloslovakia)	78
1966 - Rhone-Poulenc (Grenoble, France)	?
1968 - Coalite (Derbyshire, U.K.)	90
1976 - ICMESA (Seveso, Italy)	156

Symptoms which have been consistently observed in these acute exposures include burning sensation of mucous membranes,

headache, nausea, and vomiting (immediate symptoms); chloracne, pruritis, erythema, facial edema, and a severe type of conjunctivitis (delayed symptoms); and aching muscles of the chest and thigh, irritability, and loss of libido (persistent symptoms) (Huff et al. 1980).

In addition to these consistently observed symptoms a number of other effects have been exhibited less frequently: impaired senses and liver damage were reported in the BASF population; elevated lipid and cholesterol levels in blood were found in the Rhone-Poulenc (1956) incident; hemorrhage and central nervous system disturbances were noted in the Netherlands population; elevated blood levels of lipid and cholesterol, prediabetes, and some severe liver and neurologic damage was recorded in the Spolana (Prague) population (Huff et al. 1980, Jirasek 1973, Beiburg 1964, Suskind 1983, Kimbrough et al. 1977, Oliver 1978, UAREP 1988).

Herbicide Spraying Operations - Chronic Exposure

Most human exposure to dioxins is associated with the use of herbicides - with the herbicide Agent Orange used in Vietnam, and with the use of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) used in agriculture in the United States. Phenoxy herbicides came into commercial use as agricultural herbicides in the mid-1940's. They were used extensively and uneventfully in the control of woody and broadleaf vegatation in croplands, forests, rights-of-way and turf until about 1969, when public concern about the products was aroused by reports of spontaneous abortions in Alsea, Orgeon (AMA, 1981).

The 1976 industrial accident in Seveso, Italy alerted many people to the dangers of dioxin contamination. During that incident, a plume of reactor contents - including TCDD - rose into the air and fell in a cone-shaped pattern about a mile long and half-mile wide. Some of the persons in the area became ill immediately, while others experienced chemical burns of the skin, stomach pains and internal hemorrhage within a few days of the accident. Even more frightening was the occurrence of animal deaths and loss of vegetation in the area. Officials sealed off the area and evacuated the inhabitants (Rawls et al, 1976).

TCDD was first identified as an impurity of 2,4,5-T by Tomita et al (1959). At that time, commercially available 2,4,5-T contained anywhere from 1 to 70 ppm of TCDD. When the industry became aware of the contaminant's existence and toxicity, production operations were monitored and altered to reduce the level. By 1980 manufacturing operations were able to control the amount of TCDD in commercial formulation to less than 0.01 ppm (with occasional batches as high as 0.05 ppm) (AMA, 1981).

Agent Orange contained equal parts of 2,4,5-trichorophenoxyacetic acid (2,3,4-T) and 2,4-dichlorophenoxyacetic acid (2,4-D).

It has been estimated that about 20 million kilograms of Agent Orange was used in Vietnam. Along with 25 million kilograms of 2,4-D, it was distributed over an area of approximately 3.5 million acres (Young et al., 1978).

By the mid- to late-1970's a number of Vietnam war veterans were reported to have various medical complaints (weight loss, liver damage, recurrent skin rashes, deformed offspring, stillbirths, cancer, sterility, personality changes and "other illness") which they attributed to their exposure to Agent Orange some 8 to 18 years earlier. A class-action suit was filed against the Veterans Administration and the US Department of Defense in January 1981. At that time approximately 2.4 million veterans, including 1,200 in "Operation Ranch Hand" helicopter crews, and some 200 civilians who were involved in "dedrumming" and destroying about 40,000 55-gallon drums of surplus Agent Orange were presumably exposed (AMA, 1981). Vietnamese officials also claimed that Agent Orange exposure was implicated in hepatic cancers (Ton-That-Tuny, 1973); isolated reports of unusual soft-tissue tumors in Vietnam veterans appeared (Sarma and Jacobs, 1982).

In April 1978, the EPA had issued a notice of Rebuttable Presumption Against Registration (RPAR) for 2,4,5-T; in March 1979 the EPA imposed an emergency suspension to ban the use of 2,4,5-T in pastures, forests and rights-of-way (EPA, 1979).

Lathrop et al. (1984) evaluated the long-term health effects from occupational exposure to Agent Orange during Vietnam. In the first phase, a mortality study, findings were that no attributable excesses could be associated with exposure to the herbicide. The second phase, designed to determine morbidity incidence, also showed no definitive clinical endpoints - such as soft tissue sarcoma, porphyria, or chloracne. The Center for Disease Control performed a case-control study to attempt to identify an association between Vietnam service and subsequent male parentage of congenitally malformed offspring. The results indicated that veterans were at no greater risk than other men for siring babies with all types of serious structural birth defects (Erickson et al., 1984).

Summary of Health Effects in Humans

Epidemiological studies of exposures from PCDFs and PCDDs, whether resulting from industrial accidents or from herbicide spraying operations, have provided clear evidence that chloracne is associated with exposure. The associations between hepatological effects, neurological effects, reproductive effects, and carcinogenicity are not clear, but symptoms which have been reported include thymic atrophy, severe body weight loss, immunotoxicity, enzyme induction, effects on lipid metabolism, gastrointestinal disturbances, neurological disabilities, and porphyria.

Dermal Effects

Chloracne development in response to exposure has been demonstrated repeatedly. In the 1976 factory explosion in Seveso, a chemical cloud was released in which 2,3,7,8-tetra-CDD was concentrated. Chloracne was exhibited not only in individuals who were in the immediate vicinity during this occurrence, but also in some individuals who entered the region well after the explosion (Huff et al. 1980). Chloracne has been so consistently manifested in acute exposures that it is considered an indicator of PCDF/PCDD exposure.

Liver Effects

Hepatic porphyria, abnormal lipoprotein profiles, and abnormal biopsies have been associated with PCDD exposures at several industrial plants (Pazderova-Vejlupkova et al. 1981, Baughman, 1973).

Neurological Effects

Neurologic problems were found in individuals exposed to TCDD in the Seveso plant explosion. Since the neurologic symptoms were confined to adults and were subjective in nature (headache, dizziness, numbness) the significance of data is not clear (Kimbrough 1977, Hay 1979).

More conclusive evidence of neurologic effects were reported by Pasderova-Vejlupkova et al. (1981). This study reportedly found a 23% prevalence of peripheral polyneuropathy, and a 7% prevalence of Cranial nerve VII neuropathy in a factory population exposed to TCDD; the authors also noted that encephalopathy was suspected in some of the older workers.

Reproductive Effects

Reproductive effects have not been definitively demonstrated to be PCDF/PCDD exposure related.

Hanify (1981) investigated human birth malformations (an excess of congenital foot deformities) among a population living in an area in New Zealand that had received significant herbicide application. Although a statistical excess was found, the significance of the data was unclear since the foot deformities were the only parameter exhibiting such an excess.

No reliable evidence for increased chromosome damage, fetal wastage, or teratogenesis has found in studies of the Seveso, Italy population (Kimbrough 1972, Kimbrough et al. 1977)

No reliable evidence for increased chromosome damage, fetal wastage, or teratogenesis was found in studies of several areas in the United States where 2,4,5-T herbicide was sprayed for

deforestation (Cook 1980, Maugh 1982).

Carcinogenic effects

Evidence of carcinogenic effects have been reported in a number of epidemiologic studies; in other studies no evidence of carcinogenicity was found:

German workers exposed to trichlorophenol were found to have a statistically significant increased mortality from stomach cancer (Theiss 1982).

Male Danish workers exposed to phenoxy herbicides showed a statistically significant increase in lung cancer (Lynge 1985). Because of the small number of persons evaluated in these studies, the results are not considered conclusive evidence of carcinogenicity.

The mortality of 121 workers at a Monsanto plant in Nitro, West Virginia was evaluated. All of these workers had exhibited chloracne following exposure to 2,3,7,8-tetra-CDD. No statistical excesses in total mortality or in death from malignant neoplasms were found (Zack and Suskind 1980).

In a study of 2192 employees of Dow Chemical, workers who produced or formulated higher chlorinated phenols or derivative products were evaluated for malignant neoplasms and specific malignancies. No statistical excesses of stomach cancer, lymphomas, nasal or nasopharyngeal cancers, or malignant neoplasms was found (Cook et al., 1986).

Studies by Hardell and Sandstrom (1979), Hardell and Erickson (1981), Hardell et al. (1981), Eriksson et al. (1979, 1981) Lynge (1985) Puntoni et al (1986) Sarma and Jacobs (1981) Moses and Selikoff (1981) and Bishop and Jones (1981) indicate that 2,3,7,8-TCDD as a contaminant with other chemicals is probably carcinogenic and that exposure to it increases the incidence of soft tissue sarcoma and non-Hodgkin's lymphoma.

In a contemporary study, Hardell and Erickson (1988) compared 55 male soft tissue sarcoma (STS) patients, aged 25-80 years, with 220 living and 100 dead population-based referents. To avoid the possibility of any recall bias, another group of 190 patients (112 living and 78 dead) which had cancers other than STS, malignant lymphoma and nasopharyngeal carcinomas were included in this study. The cancer referents were of the same age group and their disease was diagnosed during the same time period as the STS patients. Results of this study indicated that exposure to 2,3,7,8-TCDD was associated with a roughly three-fold increased risk of soft tissue sarcoma. These results corroborated those reported in earlier studies conducted by Hardell and Sandstrom (1979), Ericksson et al., 1981) which associated exposure to TCDD with soft tissue sarcoma.

ANIMAL TOXICITY STUDIES

Numerous toxicological studies have documented the wide range of effects associated with exposure to PCDFs and PCDDs in animals (McConnel and Moore 1979, Poland et al. 1979, Neal et al. 1979, Poli et al. 1980, Cantoni et al. 1981, Poli et al. 1980). Oral exposure to the most toxic isomers, such as 2,3,7,8-tetra-CDD has been associated with deleterious effects to virtually every organ system. Effects which have been reported in animal studies include lethality, wasting syndrome, enzyme induction and hepatotoxicity, immunotoxicity, carcinogenicity, and reproductive and teratogenic effects.

Very few percutaneous and no inhalation exposure data are available in the toxicological literature.

A substantial body of biochemical research has shown that humans do not appear to be as sensitive as rodents to many chemicals; it is reasonable to conclude that humans might be less sensitive to some of the toxic effects of TCDD than, for instance, the guinea pig or the subhuman primate (Ayres, 1985; and Kimbrough, 1988).

Lethality

2,3,7,8-TCDD by itself is extremely toxic; along with Botulinus bacillus toxin and aflatoxin, it is one of the most lethal organic chemical compounds known to man. In terms of the acute oral dose, or LD_{50}, its toxicity ranges from 0.6 ug/kg of body weight for the guinea pig (the most sensitive of experimental animals) to 5,000 ug/kg of body weight for the hamster (which, for unknown reasons, seems unusually insensitive to PCDDs).

Single exposure of animals to oral doses of TCDD results in death within 20-40 days due to wasting syndrome, which involves progressive loss of up to 50% body weight and eventually leads to death without any clearly identifiable lethal pathological lesions. Oral acute toxicities and whole body excretion half-lifes which have been determined for a number of animal species are given below (data from Leung et al., 1988):

Animal	LD_{50} (ug/kg)	$t^{1/2}$ (days)
Guinea pig	1	30-94
Rat	22-45	31
Monkey	<70	455
Rabbit	115	-
Mouse	114	15
Dog	>300	-
Hamster	5000	15
Human	-	8 yrs

Hepatotoxicity

The liver appears to be the sensitive organ of TCDD exposure in rats and mice, and is associated with systemic hemorrhage, edema and depressed activity of the thymus.

A morphological study of liver lesions caused by TCDD exposure in rats was conducted by Jones et. al. as early as 1973. Parenchymal cell necrosis in the centrilobular zone with mononuclear cell infiltration was noted after the first week of exposure. By the second week there was dilatation of the sinusoids in the centrilobular zone, more severe inflammation and increased necrosis in the parenchymal cells; loss was not made up by hyperplasia of the live cells. Inflammation regressed after 3 to 6 weeks, but focal areas of necrosis remained around central veins and mural fibrosis of the central vein developed.

In a study conducted by Kochiba et al. (1976), young adult Sprague-Dawley rats were fed with 0.001, 0.01, or 1.0 ug of TCDD/kg 5days/week for 13 weeks. No ill effects were noted in the rats fed the 0.001 ug doses. Slight increases in relative liver weight were noted in animals fed the 0.01 ug dose. At the higher doses, a number of changes in tissue and organ function were observed. The 1.0 ug/kg/day dose caused some consumption and body weight decreases, elevated serum bilirubin and alkaline phosphatase, liver impairment, lymphoid depletion of the thymus and other lymphoid organs, and excretion of urinary porphyrins and delta-aminolevulinic acid.

In a subsequent 2-year chronic toxicity and oncogenetic study Kochiba et al. (1978) evaluated groups of female and male rats that were given oral doses of 0, 0.001, 0.01, and 0.1 ug/kg/day for 5days/week for 2 years. No toxic effects were noted in the 0.001 ug dose groups. At the 0.01 ug dose level there was slight poisoning: urinary excretion of porphyrins (in females) was increased, hepatic cellular nodules were more numerous, and there was an increased incidence of focal alveolar hyperplasia. At the 1.0 ug level, the fat and liver of the females contained 24,000 ppt of TCDD (males had an average of 8,100 ppt). Hepatocellular carcinomas were found in the females, and other tumors, such as squamous cell carcinomas of the lung, and hard palate/nasal turbinates were found. Strain-related tumors (i.e. of the pituitary, uterus, mammary glands, pancreas and adrenals) were found to be suppressed. Other toxic signs included increased mortality; decreased gain in body weight; depression of certain hematologic parameters; increased urinary excretion of porphyrins and delta-aminolevulinic aicd; increased serum activities of alkaline phosphatase, gamma-glutamyl transferase and serum glutamic pyruvic transaminase; as well as morpholocial changes in the hepatic tissues, and lymphoid and respiratory tissues.

Immunological Effects

One of the most consistent signs of TCDD toxicity in most species is thymic atrophy. The chronic studies of Kochiba et al. (1976, cited above) clearly implicated lymphoid organ involvement.

Genotoxicity and Carcinogenicity

Genotoxic effects have been evaluated in a number of genetic test systems. The results of most studies indicate that no significant genetic or cytogenetic effects were found (IARC 1982, Kociba 1984, Kimbrough and Houk 1987, Brooks 1988, UAREP 1988). In one study, clastogenic effects were reported in rats exposed to 2,3,7,8-CDD (Wahba 1988). Additionally, Whitelock (1987) demonstrated that 2,3,7,8-tetra-CDD could affect the expression of certain genes because of its ability to bind preferentially to specific promotor gene sites. Although these two studies provide evidence of some activity at the gene level, direct mutagenic interactions have not been demonstrated.

Oncogenicity was evaluated by Kochiba et al. (1976, cited above). Hepatocellular carcinomas were found, as well as evidence of squamous cell carcinomas of the lung; it was also noted that hard palate/nasal turbinates or tongue carcinomas had been induced.

In another rodent study Van Miller et al. (1977) found that as little as 5 ppt in the diet of rats induced various neoplasms. Lung and liver tumors developed at the 1 or 5 ppb level.

The National Toxicology Program conducted a carcinogenesis bioassay of 2,3,7,8-TCDD in Osborne-Mendel rats and B6C3F1 mice (NTP ,1982a). Fifty rats and 50 mice of each sex were given TCDD orally at doses of 0.01, 0.05, and 0.5 ug/kg per week (rats and male mice) or 0.04, 0.2, and 2.0 ug/kg per week (female mice). Results showed that TCDD was carcinogenic in mice: hepatocellular carcinomas were induced in males and females, and follicular cell thyroid adenomas were induced in females. Additionally, a statistically significant incidence of hepatocellular carcinomas was observed in male rats of the high-dose group (NTP, 1982a).

2,3,7,8-TCDD has also been tested in short-term tumor models as an initiator (Cohen, 1979); the results have been mixed, leading researchers to characterize the compound as varying from a very weak initiator to an inhibitor of some types of initiation.

A study sponsored by the National Toxicology Program (NTP, 1982b) found that the application of 2,3,7,8-TCDD to the skin of female Swiss-Webster mice increased the incidence of fibrosarcomas (0.005 ug was applied at a rate of 3 deciliters per week for

99 out of 104 weeks) as compared with the incidence in untreated controls. Hexachlorodibenzo-p-dioxins have also been found to be extremely potent carcinogens, producing squamous cell carcinomas after subcutaneous or intraperitoneal injection. That study is of particular interest because it demonstrated that 2,3,7,8-TCDD is a complete carcinogen in a species that is relatively resistant to acute lethality.

Reproductive and Developmental Toxicity

TCDD was first noted for its teratogenicity and fetotoxicity by Courtney et al (1970), who were testing the biological activity of 2,4,5-T in mice and rats. The herbicide sample they were using was later found to contain 30 ppm of 2,3,7,8-TCDD. The incidence of cleft palate was greater in both the C57BL/6 and AKR mouse strains, while the C57BL/6 mouse and the rat had a higher incidence of cystic kidney. All doses given the rat led to gastrointestinal hemorrhage in the fetuses; also, the increased ratio of fetal liver weight to body weight in the mouse suggested that TCDD was fetotoxic.

Although reproductive and teratogenic effects have been reported in several oral and dermal toxicity studies, the data is equivocal. Kimbrough (1972), Courtney (1977), and Giavini et al. (1982) reported that embryotoxocity resulted in rats and mice maintained on diets containing 2,3,7,8-tetra-CDD. Lamb (1984) reported that no demonstrable reproductive effects were found in male rats treated with sublethal doses of 2,3,7,8-TCDD and no teratogenic effects were observed in their offspring.

Neurotoxicity

Rodent studies have not evaluated or indicated neurologic effects in association with PCDF/PCDD exposure. One animal that is particularly sensitive to central nervous system intoxicants is the chicken. In an early study by Sanderson et al. (1981) both chicken eggs and hatchlings were treated with "environmental levels" of 2,4,5-T contaminated with 0.03 ppm TCDD. Although the general activity of the animals was unaffected, there was a dose-related increase in jumping and a retardation in visual learning (cited in AMA, 1981).

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